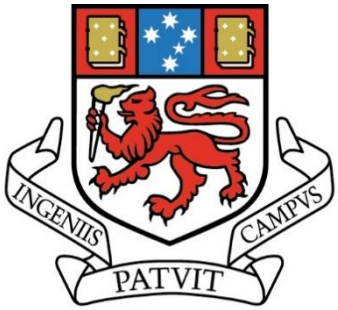

UNIVERSITY OF TASMANIA

The Effect of Chronic Benzodiazepine Use on Consumer Safety: Accidents, Injuries, and Cognitive Failures

Aneliese Poorter BA (Hons)

Submitted in fulfilment of the requirements for the Degree of
Doctor of Psychology
School of Psychology, University of Tasmania

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Aneliese Poorter BA (Hons)

5th December 2016

DECLARATION OF CO-AUTHORSHIP

Thesis title: The Effect of Chronic Benzodiazepine Use on Consumer Safety: Accidents, Injuries, and Cognitive Failures

Co-authors: Raimondo Bruno

Overall contribution: We the undersigned agree that Aneliese Poorter has made the major contribution to this work (67-100%)

Mrs Aneliese Poorter
Candidate
School of Psychology
University of Tasmania

Associate Professor Raimondo Bruno
Primary Supervisor
School of Psychology
University of Tasmania

5th December 2016

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ABSTRACT

Benzodiazepines are a class of medications with a broad range of pharmacological actions including anti-anxiety, muscle-relaxant, antiepileptic, hypnotic, and memory impairing effects. Benzodiazepines became a popular medication due to their relative safety of use and their fast-acting effects. However, increasingly research has established a range of detrimental effects, including reduced efficacy over time, and cognitive and psychomotor impairment. New benzodiazepine users commonly experience cognitive side-effects including sedation, inattention, and memory problems. In recognition of the risks of using benzodiazepines, they are rarely indicated as a first line treatment, and clinical guidelines suggest that when needed they are used for the shortest duration possible and at the lowest dose required. Despite this, there is evidence that benzodiazepine use still regularly occurs for extended durations and at high dosages within Australia. Most of the research to date has examined once-off or short duration benzodiazepine use in young, healthy, benzodiazepine-naïve individuals – a group far removed from the usual benzodiazepine using population who are more often older, have a variety of health conditions, and have used benzodiazepines regularly for an extended period of time. The current study aimed to overcome some of these gaps in the literature by examining benzodiazepine use among existing consumers, as it naturally occurs in the Australian population, specifically focusing on those who use in an ongoing, chronic manner, rather than amongst carefully selected research samples.

Understanding the impact of benzodiazepine use on experience of accidents, particularly whilst driving, is an important area of research. This thesis aimed to add to the existing accident literature by examining the influence of benzodiazepine use on a range of different incident severities including: cognitive failures (everyday cognitive slips or errors), minor injuries not requiring medical attention, and major accidents requiring medical attention. Three studies were undertaken: (1) an online, general population survey of chronic benzodiazepine users and their experiences of accidents, injuries, and cognitive failures (n=129), (2) an interview based study examining the unique effects of benzodiazepines on safety incidents in people who

inject drugs (n=170) and (3) using the same methods and population group as Study 1, the subjective experiences and perceptions of this group were explored through a qualitative design (n=129).

In both *Study 1* and *Study 3*, respondents were divided into three categories of benzodiazepine chronicity; short-term (length of use ≤ year; daily/occasional frequency), intermittent (length of use > year; occasional frequency) and chronic (length of use > year; daily frequency). Reported benzodiazepine use was often daily, of a high dosage, and for an extended period of time. For example, the chronic users in this study had on average a duration of use spanning 8 years, used most days within a month, and had an average diazepam equivalent dosage per month of 900mg. This usage is inconsistent with recommendations from current clinical guidelines. Logistic regression, used in *Study 1* showed that chronic, daily, users were at significantly increased risk of general accidents, and retrospective and prospective memory problems, compared to intermittent users. *Study 3* aimed to complement the findings of *Study 1*, by providing information about the self-reported experience, knowledge, and perceptions of chronic benzodiazepine users. Attitudes towards benzodiazepines reported in *Study 3* were mixed, although a large proportion of the sample reported negative experiences, such as dependence, withdrawal, and cognitive effects. Side-effects were regularly experienced by the group, and often did not abate, particularly for the most chronic users. Tested knowledge of benzodiazepines in the sample was low, and many respondents stated that they felt they had received inadequate information about the risks associated with benzodiazepine use. Findings from *Study 1* and *Study 3* indicate that benzodiazepines have a considerable impact on both the subjective and objective safety experiences of chronic users.

Study 2 examined the unique impact of benzodiazepine use on cognitive failures, minor injuries, and major accidents, in a group of people who inject drugs (PWID). It is recommended that benzodiazepines are best avoided in PWID, due to the high risk of dependence and additive sedative effects. However, it is known that benzodiazepines are still commonly used by PWID, and this was also evident in

Study 2. Despite the range of other substances used by this group, moderate-to-regular benzodiazepine use independently contributed to an increased risk of retrospective memory problems (OR 8.21, 95%CI 1.03-65.41, p=0.047), and major accidents (OR 3.88, 95%CI 1.20-12.50, p=0.023) after controlling for a wide range of confounders.

Overall, findings from this thesis suggest that benzodiazepine use in Australia remains inconsistent with clinical guidelines. After controlling for confounding variables, benzodiazepines had a considerable effect on safety in both the general, and a high risk population (PWID). Chronic benzodiazepine users cannot be assumed to be tolerant to the effects of benzodiazepines, and this thesis shows that they continue to experience ongoing, detrimental effects of benzodiazepine use on their safety. It is suggested that there should be more specialised services to assist those who are grappling with benzodiazepine withdrawal and dependence, and importantly to provide alternative treatments to the use of benzodiazepines. It is proposed that the use of a benzodiazepine contract, like those used for opioids, would ensure best practice prescribing occurs, and improve outcomes for both prescribers and patients.

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1 BENZODIAZEPINES – AN INTRODUCTION

CHAPTER 1: BENZODIAZEPINES – AN INTRODUCTION

Benzodiazepines are among the world's most widely prescribed psychotropic medications and are used to treat conditions such as anxiety, insomnia, panic disorders, epilepsy, muscle spasms, and alcohol withdrawal (Barker, Jackson, Greenwood, & Crowe, 2003). Common benzodiazepines prescribed within Australia are listed in Table 1. Benzodiazepines are often classified according to their half-life, that is, the time taken for the plasma concentration of a drug to decrease by half (Griffin, Kaye, Bueno, & Kaye, 2013). The general pharmacological effects of benzodiazepines include anti-anxiety, muscle-relaxant, antiepileptic, hypnotic, and memory impairing actions (Bryant, 2007). It is likely that these effects are interdependent (Curran, 1992). The pharmacological actions of benzodiazepines are outlined in Table 2.

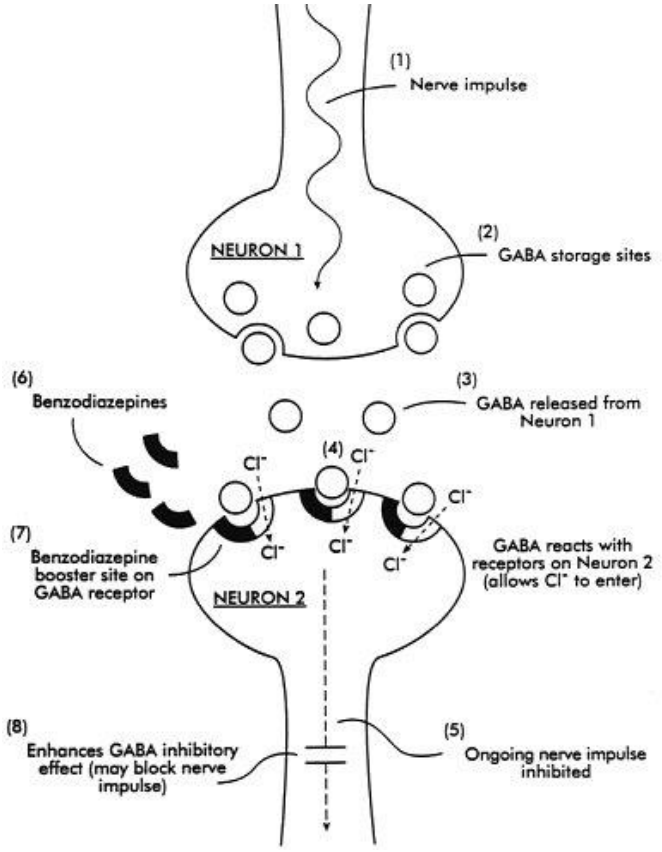
Table 1. *Common Benzodiazepines found in Australia and Classification according to Duration of Action*

Generic Name	Common trade Names
Short Duration of Action (median half-life <12 hours)	
Alprazolam	Kalma, Alprax
Oxazepam	Serepax, Murelax, Alepam
Temazepam	Temaze, Temtabs, Normison
Intermediate Duration of Action (median half-life 12-24 hours)	
Bromazepam	Lexotan
Lorazepam	Ativan
Long Duration of Action (median half-life >24 hours)	
Clobazam	Frisium
Clonazepam	Rivotril
Diazepam	Valium, Ducene, Antenex, Valpam
Flunitrazepam	Hypnodorm
Nitrazepam	Mogadon, Alodorm

Table 2. *Pharmacological Action of Benzodiazepines (Ashton, 1995).*

Pharmacological Action	Clinical Uses
Hypnotic	Short-term treatment of insomnia
Anxiolytic	Short-term treatment of anxiety
	Short-term aid to alcohol/central nervous system depressant drug withdrawal
Anticonvulsant	Status Epilepticus
	Drug-induced Convulsions
	Short-term treatment for Epilepsy
Amnesic	Premedication before surgery
	Minor surgical procedures
Muscle-relaxant	Painful muscle spasms
	Some dystonia and involuntary movements

Benzodiazepines act through potentiating the inhibitory effects of gamma-aminobutyric acid (GABA) throughout the central nervous system (Gorenstein, Bernik, & Pompeia, 1994). GABA is the main inhibitory transmitter in the brain, found at approximately 30% of all central nervous system synapses, and in many pathways and brain areas (Bryant, 2007). Benzodiazepines do not occupy the entire GABA(a) receptor but act at a modulatory site to facilitate GABA binding to the GABA(a) receptors (Bryant, 2007). More simply, benzodiazepines enhance the action of GABA, which in turn slows down central nervous system electrical signals. Figure 1 provides a diagrammatic explanation of the effects of benzodiazepines on GABA activity. The anti-anxiety effects of benzodiazepines are posited to occur due to the highly dense area of benzodiazepine binding sites in the amygdala region of the limbic system – an area often associated with the regulation of emotional behaviour (Bryant, 2007).



(1, 2) Nerve impulse causes release of GABA from storage sites on neuron 1
(3) GABA released into space between neurons
(4) GABA reacts with receptors on neuron 2; the reaction allows chloride ions (Cl-) to enter the neuron
(5) This effect inhibits further progress of the nerve impulse
(6, 7) Benzodiazepines react with booster site on GABA receptors
(8) This action enhances the inhibitory effects of GABA; the ongoing nerve impulse may be completely blocked

Figure 1. Mechanism of action of the neurotransmitter GABA (gamma-aminobutyric acid) and benzodiazepines on brain neurons (Ashton, 1995).

The popularity of benzodiazepines, in comparison to their predecessors, such as barbiturates, has resulted primarily from their initial effectiveness, combined with a relatively good safety profile. Initially, benzodiazepines were claimed to offer the advantages of lower fatality rates following overdose, lower potential for abuse, more favourable adverse effect profiles and fewer potentially serious drug interactions (Ashton, 1995; Bryant, 2007). Despite this, benzodiazepines are capable of producing a wide variety of side effects due to the broad distribution of benzodiazepine receptors found in a number of areas such as the spinal cord, cerebellum, limbic areas, and the cerebral cortex (Gudex, 1991). Additionally, benzodiazepines can have additive and synergistic effects with other central nervous system depressants including; antidepressants, antipsychotics, anticonvulsants, sedative antihistamines, and alcohol (Ashton, 1995).

Benzodiazepine Prescription Rates

Drug Utilisation Sub Committee Data

Obtaining a true indication of benzodiazepine use within the community is difficult in part due to the lack of a comprehensive prescription record. In Australia, the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS), subsidise the cost of many medications. However, some preparations are not listed on the PBS, or they are listed but a subsidy is not claimed for them, and this means that data is not collected for these medications. From 1989-2012, the Pharmacy Guild of Australia conducted an annual survey of selected pharmacies to estimate the numbers of prescriptions in non-subsidised categories. However this ceased in August 2012, meaning up-to-date data is no longer available (Department of Health, 2015). Private prescriptions are often used when pill quantity, repeat number, or clinical usage is outside of PBS indications (Australian Government Department of Human Services, 2016). As this data is not recorded, there is a significant gap in understanding benzodiazepine use within Australia. The Drug Utilisation Sub Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee collates data from PBS/RPBS prescriptions, and formerly for non-subsidised prescriptions (estimated through the Pharmacy Guild survey). The following information is based on data collected by the DUSC.

When examining the most commonly prescribed benzodiazepines listed on the PBS (whether paid for in part or fully by the patient) prescription numbers are high. In 2014, when the Australian population was estimated to be 23.5 million people (Australian Bureau of Statistics, 2014), there were the following script numbers (for all types and strengths): diazepam - 2,429,619, temazepam - 2,205,859, oxazepam - 1,063,978, and alprazolam - 304,720 (Department of Health, 2015). The highest volume individual item was temazepam 5mg tablets, which accounted for 2,164,117 scripts (Department of Health, 2015).

Approaches to Understanding Benzodiazepine Usage

Defined Daily Dose: Drug consumption is often expressed in terms of dosage, cost, or number of prescriptions. However, these measures can vary across different times and locations. To overcome this problem, the World Health Organisation developed a unit of measurement called defined daily dose (DDD). A defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults (World Health Organisation, 2011).The advantage of the DDD approach is that it provides a fixed unit of measurement that can be used to compare across samples. However, a defined daily dose is not necessarily the same as the recommended dose or a dose prescribed for a particular individual. The defined daily dose, for diazepam as an example is 10mg orally. Defined daily dosage is often presented as the DDDs/1000 population/day figure, which provides an approximate estimate of the amount of population treated daily with a particular drug. Table 3 shows DDD/1000 population/day for benzodiazepines dispensed in the community between 2012-2014 (Department of Health, 2015). This includes both scripts whose costs were covered entirely by the PBS or contributed to by the patient.

Table 3. *Benzodiazepine DDD/1000 population/day from 2012-2014 (Department of Health, 2015).*

	2012	2013	2014
Alprazolam	4.267	3.845	2.507
Bromazepam	0.004	0.003	0.003
Diazepam	5.850	5.920	6.029
Flunitrazepam	0.024	0.020	0.018
Nitrazepam	1.300	1.207	1.099
Oxazepam	1.736	1.663	1.602
Temazepam	3.484	3.426	3.236

*DDD=defined daily dose: the assumed average maintenance dose per day for a drug used for its main indication in adults

Diazepam Equivalent Dosage: Another method of understanding benzodiazepine consumption is the use of diazepam equivalent doses. Because benzodiazepines differ greatly in dose and potency, there have been attempts made to estimate equivalent dosages across the different preparations. Based on research and clinical experience, estimates are made for each preparation as to a comparative dose of diazepam. The ability to convert doses is useful in clinical practice if transfer from one benzodiazepine to another is required. In research, the simplification of various active ingredients into one standard measure allows for easier comparisons to be made (Inada & Inagaki, 2015). Whilst conversion tables are available (e.g., Ashton, 2002), they are often not in agreement, and provide only an approximate of a diazepam equivalent dose. This process does not account for other variabilities in benzodiazepines, such as time to onset and duration.

Trends in Benzodiazepine Use

Stephenson, Karanges, and McGregor (2013) investigated trends in psychotropic medication use in Australia over an 11 year period (2000-2011). Data was obtained from the Drug Utilisation Sub Committee, and included both PBS/RPBS data and estimates of non-subsidised prescriptions. Overall, the use of psychotropics in Australia increased by 58.2% during this time period; antidepressants accounted for a significant proportion of this growth. Benzodiazepines were included in both the anxiolytic (alprazolam, bromazepam, clobazam, diazepam, lorazepam, oxazepam) and sedative (flunitrazepam, midazolam, nitrazepam, temazepam, triazolam, plus Z-drugs) drug classes in this study. There was minimal change in the dispensing of anxiolytics during the study period; DDD/1000/day increased from 14.0 in 2000, to 14.9 in 2011. Dispensing of sedatives decreased from a DDD/1000/day of 9.8 in 2000, to 7.2 in 2011. Temazepam was the most commonly used sedative in 2011, accounting for 54.1% of the total sedative DDD/1000/day, although use decreased from 2000 to 2011. Overall, there were minimal changes to the dispensing rates of benzodiazepines over this 11 year period. The authors acknowledge that a problem inherent in using defined daily dose approach, is that it is quite frequently

mismatched with the usual clinical dosage, which may result in a misestimation of benzodiazepine usage.

Islam, Conigrave, Day, Nguyen, and Haber (2013) also reviewed data from the Drug Utilisation Sub Committee over a 20 year period (1992-2011). To overcome limitations with the defined daily dose approach, an additional comparison of diazepam equivalent/1000/day, using Ashton's (2002) method was conducted. An overall significant reduction (p<0.01) in benzodiazepine dispensing was found, reducing from 27.7 DDD/1000/day in 1992 to 20.8 in 2011. However, piecewise regression showed that between 2002 and 2011, this trend was significant when using the WHO DDD/1000/day measure (p<0.001), but not significant when using the Ashton diazepam equivalent (p=0.49). Whilst trends show an overall decrease in prescription of benzodiazepines, after 1992 there was an increase in quantity of private prescriptions, and the defined daily dose per prescription had on average increased. The authors suggest this may indicate that larger quantities per script are being prescribed, and private prescriptions may be used to circumvent the limitations of PBS pack sizes. Overall, data from Stephenson et al. (2013), and Islam et al. (2013) indicates that despite a plateau in benzodiazepine prescription, use remains at a substantial level within the community. This is despite recent policy changes leading to more restrictive practices regarding benzodiazepine prescription.

A fundamental problem with the use of PBS data, is that it simply indicates an item has been dispensed, but not whether it has been used, who has used it, or the method of use (e.g. as prescribed or illicit). Research suggests that the diversion of benzodiazepines to use outside of the medical context is common. The most recent National Drug Strategy Household Survey (2013), found that in those aged 18 years or older, 1.8% of males, 1.5% of females, and 1.7% of total people surveyed, had used 'tranquilisers or sleeping pills' in the last 12 months for non-medical purposes (Australian Institute of Health and Welfare, 2014). Similarly the Illicit Drug Reporting System (IDRS), found that in a national Australian sample of people who frequently

inject drugs, around two-thirds of them had recently used benzodiazepines, with fairly equal proportions reporting licit or illicit use (Stafford & Burns, 2010; Stafford, Sindicich, & Burns, 2009). The IDRS cohort is not representative of illicit drug use in the general population, but it does provide an indication of trends in people who regularly inject drugs. The use of benzodiazepines with illicit drugs is associated with adverse outcomes. For example, benzodiazepines were detected in 55% of heroin-related deaths that occurred in Victoria between 2004 and 2008 (Woods, Gerostamoulos, & Drummer, 2009). This likely reflects the additive effect between benzodiazepines and other sedatives, such as opioids, wherein their combined use results in a high risk of central nervous system depression and death (Royal Australian College of General Practitioners, 2015b). Understanding the unique effect of benzodiazepines when used illicitly, and/or in combination with illicit drugs is important to reduce associated harm.

Overall, benzodiazepines remain a commonly used class of medications throughout Australia. There is no one source of data that accurately captures benzodiazepine use; particularly usage outside of the pharmaceutical benefits scheme. Decreases in benzodiazepine use is attributed in part to the emergence of more efficacious treatments for anxiety, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). The use of SSRIs has more than doubled in use between 2000 and 2011 (Islam et al., 2013). However, the magnitude of increase in SSRIs and SNRIs has not been accompanied by the same decrease in benzodiazepine use, suggesting a straightforward replacement of medications is not occurring.

Ensuring Safe Use of Benzodiazepines

Clinical Guidelines for Prescribing

An increasing body of literature documenting negative outcomes associated with benzodiazepine use, has led to clinical guidelines that recommend limiting their prescription. The first benzodiazepine guidelines were developed in 1980

(Committee on the Review of Medicines, 1980). Over 35 years later, there have been many different iterations of these principles. Generally, guidelines recommend that the use of benzodiazepines is best avoided, or if necessary, that they should only be prescribed for the shortest time period possible and at the lowest viable dose (National Health and Medical Research Council, 1991). The Royal Australian College of General Practitioners (2000), recommends advising patients of the risks associated with use, regular reviews of continued usage, and using non-pharmacological treatments where appropriate. The recent guidelines produced by the Royal Australian College of General Practitioners (2015b), provide a thorough summary of the research to date. These guidelines outline evidence based recommendations, preferred treatment options, and provide practical materials for those prescribing benzodiazepines. The key reasons for the development of these guidelines were: (1) the risk of dependence, (2) associated cognitive and psychomotor harms, and (3) the poor efficacy with ongoing treatment. These subjects are briefly discussed here, and are elaborated on throughout this review.

Risk of Dependence: Even with normal therapeutic doses benzodiazepines are capable of producing physical and psychological components of dependence. The physical component of dependence is evidenced by tolerance (a need for increased amounts of the substance), and a withdrawal syndrome on cessation of use (Barker et al., 2003). Withdrawal from benzodiazepines is characterised by central nervous system stimulation, producing symptoms such as anxiety, sleep disorders, aching limbs, palpitations, nervousness, and seizures (Ashton, 2002). Psychological components of dependence occur when a drug becomes central to a person's thoughts, emotions, and activities, with the experience of impaired control related to their use (World Health Organisation, 2017). This dependence syndrome means that risk of benzodiazepine misuse is high; this can range from occasional use beyond the reason for prescription, to regular, high quantity recreational use (Lader, 2011).

Cognitive and Psychomotor Side-effects: It is commonly acknowledged that new benzodiazepine users will be at greatest risk of side-effects as they have not yet developed tolerance to the effects of the drug. However, side-effects do not linearly decrease with continued use, and in fact long-term users may face more insidious effects than short-term users (Lader, 2011). A review by Barker, Greenwood, Jackson, and Crowe (2005) suggests that there is a slow, but not complete recovery of cognitive function, even after extended benzodiazepine abstinence in chronic consumers. Research is increasingly examining benzodiazepines as a risk factor for cognitive decline and dementia (Gray et al., 2016; Mura et al., 2013). Throughout all stages of use, benzodiazepine patients are at an increased risk of detrimental cognitive deficits.

Low Ongoing Treatment Efficacy: It is known that tolerance to the different effects of benzodiazepines develops differentially. Tolerance is defined as a person's diminished response to a drug that results from repeated use (Hussar, 2017). The development of tolerance to benzodiazepines is discussed at length in Chapter 2. Importantly, it has become evident that benzodiazepine users can become tolerant to the intended treatment effects - making benzodiazepines unsuitable for the longer-term management of many conditions (Vinkers & Olivier, 2012).

Optimal Duration of Benzodiazepine Treatment

In addition to general prescribing guidelines for benzodiazepines, there are often recommendations made regarding the optimal length of prescribing, depending on the condition being treated. A duration of 1-4 weeks is generally recommended for benzodiazepine use, as this negates the risk of dependence and cognitive impairment (Royal Australian College of General Practitioners, 2015b).

There are also guidelines that direct practitioners in the treatment of specific conditions, based on the available evidence (for example: National Institute for Health and Care Excellence, 2014; Royal Australian College of General Practitioners, 2015b). In the treatment of insomnia and anxiety, cognitive behavioural therapies

are indicated as the first line treatment. Benzodiazepines are recommended to be used for short or intermittent use only, up to a period of four weeks, and only when other treatment options have not been successful. Conversely, in the use of acute alcohol withdrawal, benzodiazepines are usually the treatment of choice, but should only be used for a period of up to seven days (Royal Australian College of General Practitioners, 2015b).

There are few specific indications for the ongoing use of benzodiazepines. It is suggested that benzodiazepines should only be used for longer-term use when it is clearly considered that the benefits outweigh the risks. Continual risk-benefit analyses should guide the decision to use benzodiazepines as an ongoing treatment (Royal Australian College of General Practitioners, 2015b).

Chronic Benzodiazepine Use

Historically it has been argued that benzodiazepine overuse has been exaggerated, and that high prescription levels are simply attributable to the many disorders for which benzodiazepines are prescribed (Woods & Winger, 1995). However, there is some research, albeit dated, that indicates long-term benzodiazepine use occurs.

An Australian longitudinal study of 337 people aged over 75, examined participants at intake, and then three and 4.5 years post-intake and found 16.6% of participants were using benzodiazepines at all three time points (Jorm, Grayson, Creasey, Waite, & Broe, 2000). Similar evidence of long-term use has been found in other countries also. In 2008, Olfson, King, and Schoenbaum (2015) examined a prescription database covering 60% of all retail prescriptions in the United States of America. In the sample 5.2% (n=11,491,677) had filled at least one benzodiazepine prescription. The proportion of this group that were using benzodiazepines long-term (defined as use greater than 120 days) increased with age from 14.7% in 18-35 year olds, to 31.4% in 65-80 year olds. A longitudinal study of 395 Canadian benzodiazepine users interviewed respondents at two year intervals for a period of six years, beginning in 1994 (Neutel, 2005). It was found that approximately 50% of the

sample were using at more than one time point, and 16.7% of the group were using at all four time points in the study, meaning use spanned at least six years. In 2006/2007, a review of psychotropic medication use in Tasmanian residential aged care facilities was undertaken (Westbury, Beld, Jackson, & Peterson, 2010). At the initial assessment, 42% of the 2,389 aged care residents reviewed were taking a benzodiazepine regularly, and the average diazepam equivalent dose was 10.4mg per day. Twelve months later, 1,307 of these residents were re-assessed, and 62.4% were using the same dose of benzodiazepines at both time points. Regular benzodiazepine use by aged care residents, for a period of greater than nine months, has also been shown to occur in other locations including: Sydney (Snowdon & Vaughan, 1997), Canada (Hagen et al., 2005), and Norway (Selbaek, Kirkevold, & Engedal, 2008). Regular benzodiazepine use in the elderly is of particular concern due to the high risk of adverse effects, including confusion and falls. Particularly in the elderly it is recommend that regular attempts at cessation occur, as cessation is associated with positive effects including improved mobility, alertness, continence, and well-being (Gilbert, Owen, Innes, & Sansom, 1993).

These studies suggest that benzodiazepine use regularly extends far beyond the recommended four-week period. This is despite clinical guidelines being active for over thirty-five years. It would be expected that a reduction in chronic benzodiazepine prescribing in response to these guidelines, would have occurred by now, if it were going to. Future research cannot simply extend the results of acute benzodiazepine studies to chronic users, but must work to understand the unique impact of ongoing benzodiazepine use.

2 The Acute and Chronic Effects of Benzodiazepines

CHAPTER 2: THE ACUTE AND CHRONIC EFFECTS OF BENZODIAZEPINES

Acute Effects of Benzodiazepine Use

Cognitive and Psychomotor Impairment

In respect to benzodiazepine studies, acute effects are those that occur rapidly following a single or brief dosing regimen usually in benzodiazepine-naïve patients. Whilst it is widely accepted that the short-term use of benzodiazepines can produce desirable anxiolytic, sedative, muscle-relaxant, and anticonvulsant effects (Barker et al., 2003), there are also a considerable range of side-effects associated with short-term use (Table 1). Effects that are considered adverse are dependent on reason for prescription, for example sedation may be a desired effect before surgery however, would be unwanted in a patient using a benzodiazepine for daytime anxiety. Most of the adverse effects associated with acute benzodiazepine use are extensions of the desired action of the drug, for example; drowsiness, ataxia, fatigue, confusion, weakness, and vertigo (Vgontzas, Kales, & Bixler, 1995). Benzodiazepines can also occasionally cause paradoxical stimulant effects such as increased anxiety, insomnia, nightmares, hypnogogic hallucinations at sleep onset, irritability, hyperactive or aggressive behaviour, and exacerbation of seizures in people with epilepsy (Ashton, 1995; Jones, Nielsen, Bruno, Frei, & Lubman, 2011).

Table 1. *Common Side-Effects of Benzodiazepines (Barker et al., 2003).*

Side-Effects		
Aggression	Flushing	Muscle Cramps
Agitation	Gastrointestinal Complaints	Nausea
Anorexia	Genito-urinary complaints	Palpitations
Bitter or metallic taste	Hallucinations	Panic
Bizarre, abnormal behaviour	Headache	Paranoid ideation
Constipation	Hiccups	Shortness of breath
Delirium	Libido changes	Swollen Tongue
Depression	Increased appetite	Tachycardia
Dry mouth	Increased Salivation	Visual Disturbances
Dysarthria	Joint pain	Vivid dreams
Failure to ovulate	Menstrual irregularities	Weight Loss

A review by Buffett-Jerrott and Stewart (2002) suggests that the most commonly occurring cognitive effects of short-term benzodiazepine use are sedation, inattention, and amnesia. Most of the reviewed studies included acute doses of benzodiazepines in healthy people, without a history of benzodiazepine use. Table 2 presents a summary of the main cognitive areas investigated by Buffet-Jerrott and Stewart. The authors conclude that there are detrimental and independent effects of acute benzodiazepine use on sedation, attention, and memory capacity; however, they do acknowledge that these effects do not continue linearly as benzodiazepine use progresses.

A similarly timed review (De Visser et al., 2002) examined the effect of benzodiazepine use in healthy volunteers. The review only included studies that used benzodiazepine doses targeted for anxiety. Benzodiazepine doses were pooled into one of three categories: 'low', 'medium', or 'high'. The 'medium' category represented doses that were the lowest recommended therapeutic dose for that particular preparation. 'Low' and 'high' doses were those under and above this level respectively. A total of 56 studies were included, and the 173 different tests used were divided into neuropsychological tests, subjective measures, and neurophysiological measures. In order to summarise the findings, the neuropsychological tests were separated into core domains. These domains were: achievement, attention, executive function, memory, visual/motor, and motor. There were 58 different subjective assessments used, and clustering techniques found that scales measuring 'alertness', 'mood,' and 'calmness' were most commonly used. Neurophysiological measures included electroencephalograms (EEG), eye movement, evoked potential, and startle reflex tests. Approximately one-third of all the tests used did not show any response to benzodiazepine dosing. However there was a dose dependent effect of benzodiazepine use: 'high' doses of benzodiazepines caused impairment across almost all categories (Table 3).

Table 2. *The Effect of Acute Doses of Benzodiazepines on Cognition in Benzodiazepine-Naïve Individuals (As reviewed by: Buffett-Jerrott and Stewart, 2002).*

Area of cognition	Sub-area	Description *(examples of measures used)*	Review conclusion *(BZD=Benzodiazepine)*	Studies reviewed
Sedation	Subjective	Self-rated measures of sedation, often using visual analogue scales.	BZDs induce subjective feelings of sedation	Allen, Curran, and Lader (1991); Buffett-Jerrott, Stewart, Bird, and Teehan (1998); Danion, Zimmermann, Willard-Schroeder, Grange, and Singer (1989); Stewart, Rioux, Connolly, Dunphy, and Teehan (1996)
	Objective: - Experimental tests	Cognitive processing and psychomotor speed (Digit Symbol Substitution Task, Discriminant Reaction Time Task, Finger Tapping Test)	Impaired by BZD use	Bishop, Curran, and Lader (1996); Boulenger et al. (1989); Curran and Gorenstein (1993); Curran, Pooviboonsuk, Dalton, and Lader (1998); Curran, Schifano, and Lader (1991); Curran, Schiwy, and Lader (1987); Danion et al. (1990); Fang, Hinrichs, and Ghoneim (1987); Preston et al. (1988)
	Objective: - Physiological measures	Biological indications of sedation (saccadic eye movements, Critical Flicker Fusion Threshold)	Impaired by BZD use	Curran et al. (1998); Green, McElholm, and King (1996); Lucki, Rickels, and Geller (1986); Preston et al. (1988)
Attention	Focused/execute attention	Ability to direct attention to a stimuli (symbol, letter or digit cancellation tasks)	Impaired by BZD use	Coull, Middleton, Robbins, and Sahakian (1995); Fang et al. (1987); Vidailhet et al. (1994); Vidailhet, Kazes, Danion, Kauffmann-Muller, and Grange (1996)
	Sustained attention	Ability to attend to a stimulus and maintain focus over time (List Repetition Task)	Impaired by BZD use	Fleishaker, Garzone, Chambers, Sirocco, and Weingartner (1995); Hommer, Weingartner, and Breier (1993); Weingartner, Hommer, Lister, Thompson, and Wolkowitz (1992)
	Encode attention	Ability to perform multiple mental manipulation tasks (Paced Auditory Serial Addition Task, Digit Span)	Impaired by BZD use	Buffett-Jerrott, Stewart, Bird, et al. (1998); Fluck et al. (1998); Preston et al. (1988)

Area of cognition	Sub-area	Description *(examples of measures used)*	Review conclusion *(BZD=Benzodiazepine)*	Studies reviewed
	Shift attention	Ability to shift attention between tasks (Posner's cued visual search paradigm)	Impaired by BZD use	Carter, Maddock, Chaderjian, and Post (1998); Johnson, Weingartner, Andreason, and George (1995)
	Divided attention	Ability to perform two or more tasks at once (dual tasks, e.g. word pair learning plus visual discrimination task)	No BZD impairment	Gorissen and Eling (1998)
Memory	Sensory memory	Brief sensory impressions that remain after a stimulus is no longer present	N/A	No studies completed at time of review
	Short-term memory	Memory occurring whilst actively attending to a stimulus (digit span test)	No BZD impairment	Boulenger et al. (1989); Curran et al. (1987); Sellal et al. (1992)
	Long-term memory	Information stored for later use	BZDs impair anterograde amnesia (information acquired after drug ingestion)	Curran (1986)
	Long-term memory - Explicit memory	Occurs when the participant is aware that their memory is being tested, and a conscious effort to remember is made (free recall, cued recall, and recognition memory tasks)	Impaired by BZD use	Boulenger et al. (1989); Buffett-Jerrott, Stewart, Bird, et al. (1998); Buffett-Jerrott, Stewart, and Teehan (1998); Curran et al. (1994); Curran et al. (1987); Eves, Curran, Shine, and Lader (1988); Gorissen, Curran, and Eling (1998); Legrand et al. (1995); Weingartner et al. (1992); Weingartner, Rawlings, George, and Eckardt (1998)
	Long-term memory - Implicit memory	The participant is not aware that memory is being tested, and does not consciously attempt to remember (word-stem completion task, picture-fragment completion task)	Impaired by BZD use	Bishop et al. (1996); Brown, Brown, and Bowes (1989); Buffett-Jerrott, Stewart, Bird, et al. (1998); Buffett-Jerrott, Stewart, and Teehan (1998); Curran and Gorenstein (1993); Fang et al. (1987); Fleishaker et al. (1995); Greenblatt, Shader, Divoll, and Harmatz (1981); Legrand et al. (1995); Sellal et al. (1992); Stewart et al. (1996); Vidailhet et al. (1994)

Table 3. *The Effects of Acute Benzodiazepine Use on Neuropsychological Functioning (As reviewed by De Visser et al., 2002)*

Neuropsychological Domain	All Doses	Low[a]	Medium[b]	High[c]
Achievement	=	=	N/A	N/A
Executive	↓	=	=	=
Attention	↓	=	=	↓
Memory	↓	=	=	↓
Visual/motor	↓	↓	=	↓
Motor	=	=	=	=
Subjective	↓	=	=	↓
Physiological	↓	=	↓	↓

Low, Medium and High refer to whether the dose studied was either [a]below, [b]equal to, or [c]above, the recommended therapeutic dose for each particular preparation. ↓ Performance decreased when exposed to benzodiazepines, and 95%CI *did not* cross zero. = Performance decreased when exposed to benzodiazepines, but 95%CI crossed zero. N/A - Not Assessed

Limitations of Investigating Acute Doses

Much of the research to date examines a single benzodiazepine dose in a naïve user. This information is useful to understand the effects on a person newly prescribed benzodiazepines, but these results cannot be generalised to those who are taking the medication regularly over a longer period. This is due in part to the development of tolerance to the drug's effects. Tolerance occurs when a greater amount of the medication is required to produce the same effects, and may often lead to increased dosages, and thus prescriptions, being used to maintain the therapeutic effect (Royal Australian College of General Practitioners, 2015a). Development of tolerance to the various effects of benzodiazepines does not develop at an equal rate; the various actions are briefly reviewed below.

Sedative and Hypnotic Effects: It is commonly accepted that tolerance to the sedative effect of benzodiazepines develops quite rapidly over 1-2 weeks, as observed by sleep patterns and reported daytime sleepiness. This effect occurs more slowly in the elderly due to slower metabolism and susceptibility to central nervous system depression (Ashton, 1995; Barker et al., 2003; Curran, 1992).

Tolerance to sedative effects appears to occur most frequently in benzodiazepines with a short half-life (Vinkers & Olivier, 2012).

Anticonvulsant Effects: Tolerance to the anticonvulsive effects can also occur in a short period of time (less than 6 months), which makes benzodiazepines unsuitable for the long term treatment of epilepsy (Barker et al., 2003). Using on an intermittent schedule may reduce the development of tolerance in these patients (Vinkers & Olivier, 2012).

Amnestic Effects: Complete tolerance to the amnestic effects does not appear to occur. Episodic memory is impaired in long-term users, whilst semantic memory, immediate memory and long-term memory are less affected (Ashton, 1995; Curran, 1992). Short-term memory continues to be affected after an acute benzodiazepine dose in chronic users (Curran et al., 1994; Lucki et al., 1986). A major concern is that memory loss associated with benzodiazepine use may persist beyond the duration of use (Barker, Greenwood, Jackson, & Crowe, 2004b; Tata, Rollings, Collins, Pickering, & Jacobson, 1994).

Anxiolytic Effects: Whilst research is divided, it is likely that a slow tolerance to the anxiolytic effects of benzodiazepines occurs. Some authors suggest that this means benzodiazepines are unsuitable for the treatment of anxiety over a period greater than 4 months (Ashton, 1995). Curran (1992) found that in her population of chronic benzodiazepine users (average length of use of 10 years), a regular daily dose of a benzodiazepine led to significant increases in ratings of contentedness and calmness, and a decrease in state anxiety scores (as measured by the Spielberg Inventory). Curran states this may indicate tolerance to anxiolytic effects does not occur. However she also acknowledges that these findings could be explained by a heightening of anxiety immediately before a dose (as withdrawal occurs), thus leading to a significant decrease afterwards. It is also possible that simply taking a pill has a placebo effect leading to reduction in anxiety.

Despite an understanding that tolerance does develop differentially with benzodiazepine use, the exact mechanism by which this occurs is unclear. Whilst it is often assumed that benzodiazepine users are less at risk from acute effects after the first few weeks of dosing, it is likely that personal characteristics will complicate the development of tolerance (Vinkers & Olivier, 2012). It is possible that tolerance may develop more quickly to the therapeutic effects compared to the side-effects. As such, further research is required to understand the impact of tolerance in day-to-day situations. The complex and individual development of tolerance means that acute and chronic users of benzodiazepines are not affected comparably.

Cognitive Effects of Chronic Benzodiazepine Use

As outlined above, the effects of long-term benzodiazepine use cannot simply be generalised from the known acute effects. However the existing research examining long-term benzodiazepine users is difficult to evaluate due to a variety of methodological issues. At the simplest level, there is often no distinction made between the different benzodiazepines, which can differ greatly in their pharmacokinetic properties. Much of the research to date is plagued by methodological issues such as small sample sizes, the use of poly-drug using subjects, the likelihood of anxiety and other pathology, and lack of double-blind, placebo controlled studies (Barker et al., 2005; Barker et al., 2003). Another difficulty is the wide range of different cognitive measures that are employed. The discrepancy in what is considered ‘long-term’ also makes research particularly difficult to integrate; use has ranged from 12 weeks (Romach et al., 1991) to in excess of 5 years (Gorenstein et al., 1994). Many studies do not consider length of time since last dose, meaning that any effects found may be due to acute or post-acute drug effects, rather than a true ‘long-term’ effect (Barker, Greenwood, Jackson, & Crowe, 2004a). Similarly, studies often use a single testing time to investigate deficits; however, research by Ghoneim, Mewaldt, and Hinrichs (1984) found that multiple test times were more likely to reveal deficits that may be

masked on a single test occasion. Despite these difficulties there have been some attempts to summarise the findings of research to date.

Barker and colleagues (2004a) undertook a meta-analysis of the research examining long-term benzodiazepine use and cognitive functioning. In order to make comparisons across studies, the average daily doses of benzodiazepines reported were converted to an equivalent diazepam dose. Length of benzodiazepine use ranged from 1-24 years (*mean*=9.9 years). Thirteen studies met inclusion criteria for the analysis, which included a total of 45 different cognitive tests. Each test and the cognitive function measured was grouped into one of 12 broad categories of cognitive function as identified by Lezak (1995), and Spreen and Strauss (1998): sensory processing, non-verbal memory, speed of processing, attention/concentration, general intelligence, working memory, psychomotor speed, visuospatial ability, problem-solving, verbal memory, motor control/performance, and verbal reasoning. The meta-analysis found moderate-to-large effect sizes of benzodiazepines across each domain of cognition (Table 4), with none having a 95% confidence interval spanning zero. The authors concluded that long-term benzodiazepine users are impaired across many cognitive areas and that this impairment appears to be a generalised rather than specific effect.

Table 4. *Meta-Analysis Results: Effects of Long-Term Benzodiazepine Use on Cognitive Function (Barker et al., 2004a).*

Cognitive Function Category	Cohen's *d*	Weighted effect size *d*	SD of weighted *d*
Sensory processing	-0.84	-1.30	0.69
Psychomotor speed	-1.10	-0.99	0.67
Nonverbal memory	-1.18	-0.91	0.45
Visuospatial	-1.12	-0.86	0.39
Speed of processing	-0.76	-0.72	0.31
Problem Solving	-0.63	-0.68	0.16
Attention/concentration	-0.65	-0.67	0.40
Verbal memory	-0.58	-0.66	0.40
General Intelligence	-0.70	-0.64	0.28
Motor Control/ Performance	-0.45	-0.49	0.36
Working Memory	-0.48	-0.48	0.33
Verbal Reasoning	-0.21	-0.42	0.29
Overall	-0.72	-0.74	0.25

SD=Standard Deviation

Residual Effects of Benzodiazepines

Evidence remains conflicted about the degree to which the negative effects of benzodiazepines may persist beyond the withdrawal period. Two meta-analyses by Barker, Greenwood, Jackson & Crowe (2004b), examined the recovery of function in long-term benzodiazepine users, and performance compared to controls. Both analyses used the same 12 cognitive categories as in the aforementioned study of current chronic users (Barker et al., 2004a). Key characteristics of these three samples are outlined in Table 5. Analysis A compared the cognitive performance of long-term benzodiazepine users, before and after ceasing use. Results for each cognitive category are shown in Table 6. Overall, effect sizes were positive which indicates a recovery of function. 95% confidence intervals spanned zero for 6 out of the 11 areas of cognition, suggesting results should be interpreted with caution; however, the authors conclude the direction and magnitude of the effect sizes should not be disregarded. Analysis B compared the cognitive performance of previous long-term benzodiazepine users, to normative data or control subjects (a

mix of normal and anxious controls). With the exception of sensory processing, all effect sizes were negative, meaning that previous benzodiazepine users performed more poorly than controls (Table 7). 95% confidence intervals did not span zero for 8 out of 11 categories, suggesting that these effects are statistically significant.

Table 5. *Meta-Analyses examining Cognitive Function in Long-Term and Previous Benzodiazepine Users*

Study Characteristics	Barker et al. (2004a)	Barker et al. (2004b)	
		Analysis A	Analysis B
Comparison groups	LT BZD[a] users; controls	Pre- and Post-withdrawal;	Abstinent LT BZD users; controls
Number of studies	13	10	9
Sample size	384	297	284
Percentage; males	40.6%	37.1%	38.7%
Mean age; years (range)	47.6 (21-75)	47.1 (21-75)	42.7 (21-75)
Mean length of BZD use; years (range)	9.9 (1-34)	10 (1-29)	8.9 (1-29)
Mean daily BZD dose; milligrams[b] (SD[c])	17.2 (9.86)	15.3 (18.9)	16.7 (21.1)
Time between testing[d]; months (range)	N/A	3 (1-65)	3 (1-65)

[a]LT=long-term, BZD=benzodiazepine. [b]Diazepam equivalent dose. [c]SD=Standard Deviation. [d]Median time between withdrawal and assessment

Table 6. *Meta-Analysis Results: Recovery of Cognitive Function in Abstinent Long-Term Benzodiazepine users (Barker et al., 2004b).*

Cognitive Function Category	Cohen's *d*	Weighted effect size *d*	*SD* of weighted *d*
Sensory processing	0.47	0.37	0.46
Psychomotor speed	0.51*	0.50	0.15
Nonverbal memory	0.42*	0.34	0.29
Visuospatial	0.67*	0.70	0.12
Speed of processing	0.35	0.32	0.44
Problem Solving	0.64*	0.64	n/a^
Attention/Concentration	0.69*	0.69	0.48
Verbal memory	0.44	0.36	0.46
General Intelligence	0.58*	0.62	0.21
Motor Control/ Performance	0.28	0.21	0.27
Working Memory	0.19	0.15	0.22
Verbal Reasoning	0.08	0.06	0.07
Overall	0.42*	0.41	0.22

SD=Standard Deviation. *95%CI does not span zero. ^only one problem-solving test was used.

Table 7. *Meta-Analysis Results: Cognitive Function in Abstinent Benzodiazepine users Compared to Controls (Barker et al., 2004b).*

Cognitive Function Category	Cohen's *d*	Weighted effect size *d*	*SD* of weighted *d*
Sensory processing	0.48	0.26	0.34
Psychomotor speed	-0.87*	-0.78	0.60
Nonverbal memory	-0.36*	-0.26	0.10
Visuospatial	-0.30*	-0.49	0.45
Speed of processing	-0.59*	-0.76	0.55
Problem Solving	-0.11*	-0.11	n/a^
Attention/Concentration	-0.63*	-0.43	0.41
Verbal memory	-0.89*	-2.50	0.88
General Intelligence	-0.34*	-0.47	0.23
Motor Control/ Performance	-0.65*	-0.62	0.04
Working Memory	-0.46	-0.58	0.42
Verbal Reasoning	-0.05	-0.02	0.05
Overall	-0.41*	-0.48	0.45

SD=Standard Deviation. *95%CI does not span zero. ^only one problem-solving test was used.

Comparing these three meta-analyses by Barker and colleagues (Barker et al., 2004a, 2004b), clarifies the cognitive impact of long-term benzodiazepine use (summarised in Table 8). There were moderate-to-large effects sizes of current long-term benzodiazepine use on all areas of cognitive function. Whilst cessation of long-term benzodiazepine use was associated with some recovery of function, this recovery in most instances was not equivalent to the performance of control subjects/normative data. Particularly, psychomotor speed and verbal memory were associated with a small recovery of function, and a large effect size indicated substantial residual impairment remains relative to controls. The small number of studies suitable for inclusion in these analyses led the authors to conclude that whilst results should be interpreted with caution, they are likely a conservative estimate of deficits experienced. Results support ceasing benzodiazepine use to reduce cognitive deficits. With deficits remaining for a period of at least 6 months, caution should be applied in the longer-term use of benzodiazepines.

Table 8. *Summary of Meta-Analytic findings from Barker et al., (2004a; 2004b)*

Cognitive Function Category	LT BZD[a] users impaired[b]	Recovery of function occurs after cessation of BZD use[c]	Residual impairment remains, compared to controls[c]
Sensory processing	✓		
Psychomotor speed	✓	✓	✓
Nonverbal memory	✓	✓	✓
Visuospatial	✓	✓	✓
Speed of processing	✓		✓
Problem Solving	✓	✓	✓
Attention/Concentration	✓	✓	✓
Verbal memory	✓		✓
General Intelligence	✓	✓	✓
Motor Control/ Performance	✓		✓
Working Memory	✓		
Verbal Reasoning	✓		
Overall	✓	✓	✓

[a]LT=long-term, BZD=benzodiazepine; [b]Barker et al., 2004a; [c]Barker et al., 2004b ✓=statistically significant result (95%CI did not cross zero).

In an attempt to overcome some of the limitations of the studies used in their previous meta-analyses, Barker et al., (2005) conducted a study comparing previous benzodiazepine users who had been abstinent for at least 6 months, to well-matched comparison groups, on a limited number of cognitive measures. The 20 benzodiazepine using participants were each matched to two benzodiazepine-naïve controls; one who had been diagnosed with anxiety, and one who had not. The benzodiazepine users had a mean diazepam equivalent of 33.1mg (*SD*=32.8, range=7.5-160). The mean length of use was 108.5 months (*SD*=95.5, range=12-348) and mean length of abstinence was 42.2 months (*SD*=50.8, range=6-174.5). Five cognitive areas were studied: attention/concentration, motor control/performance, non-verbal memory, verbal memory, and visuospatial skills. Significant, moderate-to-large magnitude impairments were found for benzodiazepine users on verbal memory (*d*=-1.43), and motor control (*d*=-1.33) compared to both control groups (Barker et al., 2005). The anxious and control groups performed similarly and significantly better than the benzodiazepine group, suggesting that benzodiazepine use, rather than any confounding factor such as anxiety, was likely responsible for the difference in performance (Barker et al., 2005). Mean effect sizes for each category were also compared to the effect sizes found in the earlier meta-analysis examining long-term follow-up (Barker et al., 2004b). Rank order from largest to smallest effect size was very similar across the two studies, with both identifying verbal memory as the cognitive function most affected by previous benzodiazepine use.

Health Consequences of Long-Term Benzodiazepine use

In addition to the cognitive deficits associated with long-term benzodiazepine use, there is evidence that there are other health sequelae associated with chronic use. Understanding this association is complicated by the fact that many people who use benzodiazepines already have poor physical or mental health. Furthermore, overlap between withdrawal symptoms and affective/anxiety disorders, can make differential diagnosis of symptoms complicated. One area that is currently of high

interest is the possible link between benzodiazepine use and dementia; between 1998 and 2015, there were 11 observational studies examining this association. Pariente, de Gage, Moore, and Bégaud (2015) reviewed these studies, and concluded that there was one study that showed a protective effect of benzodiazepine use on development of dementia (Fastbom, Forsell, & Winblad, 1998), one with no association between the two (Imfeld, Bodmer, Jick, & Meier, 2015), whilst nine showed a detrimental association between benzodiazepine use and the development of dementia (Billioti de Gage et al., 2014; Billioti deGage et al., 2012; Chen, Lee, Sun, Oyang, & Fuh, 2012; Gallacher et al., 2012; Lagnaoui et al., 2002; Lagnaoui et al., 2009; Wu, Ting, Wang, Chang, & Lin, 2011; Wu, Wang, Chang, & Lin, 2009). A problem inherent in these studies is that allocation to the group is not random, and a causal direction cannot be assumed. The mechanism by which benzodiazepines may be associated with dementia is unknown, and although there are several theories, these will remain speculative until there is more comprehensive research. Pariente et al. (2015) conclude that there is no established association between dementia and the short-term use of benzodiazepines (i.e. less than three months). This is important from a clinical viewpoint, and is another piece of evidence to support limiting the use of benzodiazepines to short time periods only.

Summary

The acute effects of benzodiazepines that occur after a single or brief dosing regimen are most commonly sedation, inattention, and amnesia. However, there are dose-dependent effects, and higher doses effect a range of cognitive functions. Tolerance to benzodiazepines occurs differentially for the various actions, thus the effects of benzodiazepines on chronic users cannot simply be assumed from the acute effects. Meta-analyses suggests that there is a generalised effect of long-term benzodiazepine use on cognition, and that there is some but not a complete recovery of function after a period of abstinence.

3 Benzodiazepines and Driving

CHAPTER 3: BENZODIAZEPINES AND DRIVING

Current evidence suggests that long-term benzodiazepine use results in various cognitive impairments. Considering this and given that the prevalence of benzodiazepine use is high and often inconsistent with therapeutic guidelines, there has been increasing attention paid to the effects that benzodiazepines have on safety in day-to-day living. An area of particular interest has been the impact on driving ability, which is a task with high psychomotor and cognitive demands. Benzodiazepine users are commonly urged to be cautious when undertaking activities such as driving, but are required to self-monitor their capacity to drive safely (Figure 1).

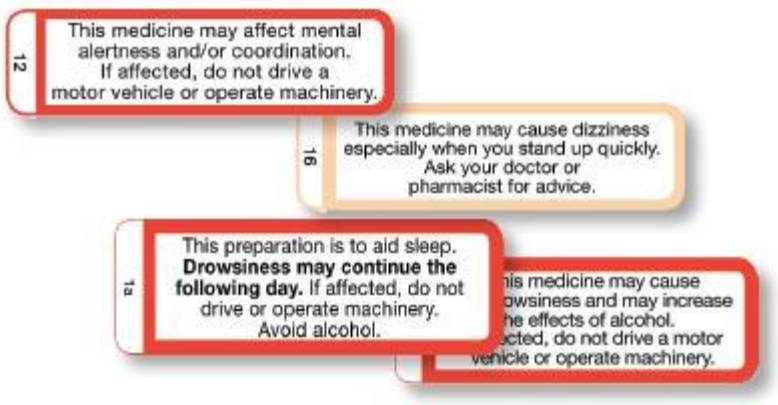


Figure 1. Medication Labels required when Benzodiazepines are dispensed in Australia.

Whilst the impairment that alcohol causes to driving ability is widely understood, it is only more recently that awareness about drug-driving has increased. Research examining drugged driving has used many methods including: telephone surveys of general populations, examining drivers held by police for 'impaired' driving, driving simulator studies, laboratory testing of relevant psychomotor skills, on-road driving tests, and internet surveys of specific populations. For a comprehensive list of the studies examining drug driving, see Kelly, Darke, and Ross (2004). Research relevant to benzodiazepines and driving will be briefly reviewed here.

Epidemiological Research

Epidemiological research frequently examines blood samples of drivers involved in an accident or apprehended for impaired driving. This provides information about what drugs may have been used by the individual, but does not establish a causal relationship. A review by Kelly, Darke, and Ross (2004) examined all studies investigating drug use and driving completed post 1970. Across the studies reviewed, it was found that for drivers involved in motor vehicle accidents, cannabis was generally the most commonly detected drug (2-32%), followed by benzodiazepines (2-15%), cocaine (4-11%), amphetamines (2-6%), and opioids (3-5%). For drivers detained for 'driving under the influence', cannabis was again the most prevalent drug, followed by benzodiazepines. Benzodiazepines were detected in drivers suspected or arrested for driving under the influence in higher rates (30-65%) in Denmark, Norway, Switzerland, Scotland and the Netherlands, and lower rates (5-20%) were found in Australia, Finland, Slovenia, Northern Island, Sweden and the United States.

A systematic review by Dassanayake, Michie, Carter, and Jones (2011) examined the effect of benzodiazepines, opioids, and anti-depressants, on driving ability. Research published between 1966 and 2010 was reviewed, and included both epidemiological studies (*n*=21), and experimental studies (*n*=69). Epidemiological research examining the association between benzodiazepine use and accidents were divided into case control studies (*n*=13), and cohort-studies (*n*=8). The meta-analyses found that benzodiazepine users were 60-80% more likely to be involved in traffic accidents (for case-control studies: 59%, pooled OR 1.59; 95%CI 1.10-2.31, and for cohort studies: 81% pooled incidence rate ratio 1.81; 95%CI 1.35-2.43). When benzodiazepines were combined with alcohol, the risk of an accident was increased seven-fold (pooled OR 7.69; 95%CI 4.33-13.65).

The Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID) project, aimed to bring together experienced organisations in Europe, to provide a coordinated set of research and resources to combat the problems associated with

driving under the influence of substances. Epidemiological research data was gathered across 15 countries, during 2007-2009 (Houwing et al., 2011). General prevalence rates of substances detected in drivers, was collected from 48,545 drivers randomly stopped in 13 countries. Participation was voluntary, and samples were collected of either saliva, blood, or both. The voluntary nature means research may have been susceptible to non-response bias, whereby drivers who knew they were under the influence of a substance were less likely to participate. Alcohol was the most commonly detected substance in the sample, found in 3.48% of those tested, followed by illicit drugs (1.90%) and medicinal drugs (1.36%). Benzodiazepines were detected in 0.9% of the drivers tested. These figures represent substances that were detected on their own, not in combination with another substance.

In another DRUID project, drivers injured or killed in a car accident were tested for traces of substances (Isalberti et al., 2011). Data on seriously injured drivers (*n*=3,570) was collected from six countries, and for fatally injured drivers (*n*=1,293) from four countries. As expected, alcohol was the most regularly detected substance in both injured and killed drivers. In injured drivers, benzodiazepines were detected in a range between 0% (Netherlands) and 10.2% (Finland), and alongside cannabis, were the most commonly detected substances following alcohol. In the vast majority of these cases, benzodiazepines were detected in combination with alcohol, cannabis, amphetamines, and medicinal opioids. Detection rates in deceased drivers were similar, with the highest benzodiazepine detection rate again occurring in Finland (13.3%). After alcohol, benzodiazepines were the most commonly detected drug in these deceased drivers. Interestingly, amongst males, the highest detection of benzodiazepines occurred in the 25-34, and 35-49 year age groups, whilst in females, the highest rate occurred in those aged 50 years and over. There was a low rate of female subjects (17%), so these findings should be interpreted cautiously, but they may reflect differing patterns of benzodiazepine usage amongst different genders. In fatally injured drivers, benzodiazepines were commonly found in association with alcohol, amphetamines,

cannabis, and z-drugs (zolpidem and zopiclone). Estimates in the DRUID samples are likely to be conservative, as concentration cut-offs were chosen for blood samples, and if a blood sample was below the cut-off it was considered to be negative.

Data from these two DRUID studies was then used to calculate the 'relative risk' of being seriously or fatally injured whilst positive for a substance. Relative risk is defined as the ratio of two risks; the risk of an event occurring in the group of exposed subjects and the risk of the event occurring in the group of non-exposed subjects. The risk estimate for those using benzodiazepines/Z-drugs, of being seriously injured was 1.99 (95%CI: 1.36-2.91) and fatally injured was 5.40 (95%CI: 3.90-7.46). Based on the assessments of the odds ratio for injured and killed drivers, the authors compiled an estimate of risk for each substance class (Table 1). Benzodiazepines/Z-drugs fell in the medium risk category. Also in this category was a blood alcohol concentration greater than 0.5g/L; this blood alcohol level is equivalent to the 0.05% blood alcohol concentration that is used as a legal cut-off for safe driving in Australia. If this level of alcohol intoxication is considered dangerous, it does pose the question as to why driving under the influence of benzodiazepines, that has an equivalent level of risk, remains legal.

Table 1. *Relative Risk of getting Seriously Injured or Killed when using Various Substance groups (Hels et al., 2011).*

Risk Level (Injury or Fatality)	Risk OR[a]	Substance Group
Slightly increased risk	1-3	≥0.1<0.5g/L alcohol in blood
		Cannabis*
Medium increased risk	2-10	≥0.5<0.8g/L alcohol in blood
		Cocaine*
		Illicit or medicinal Opiates*
		Benzodiazepines and Z-drugs*
Highly increased risk	5-30	≥0.8<1.2g/L alcohol in blood
		Amphetamines*
		Multiple Drugs*
Extremely increase risk	20-200	≥1.2g/L alcohol in blood
		Alcohol in combination with drugs*

[a]Risk Odds Ratio= Relative risk is defined as the ratio of two risks; the risk of an event occurring in the group of exposed subjects and the risk of the event occurring in the group of non-exposed subjects. The relative risk estimates were approximated to odds ratios. *This includes concentrations in blood/saliva detected at or above the relevant cut-off point; this does not indicate whether use was acute or ongoing.

Prevalence studies have been extended upon by determining the responsibility of drivers involved in accidents. Culpability has been attributed in many Australian studies by using a method established by Robertson and Drummer (1994). This method involves identifying mitigating factors, such as road condition, and depending on the presence of these mitigating factors, drivers are deemed fully, partly, or not culpable. A meta-analysis by Dassanayake et al. (2011) examined whether benzodiazepines were more commonly detected in the blood of drivers who were responsible for an accident, compared to those who were not. This meta-analysis used six case-control studies, including large population studies from Longo, Hunter, Lokan, White, and White (2000), involving 2,500 crash injured South Australian drivers, and Drummer et al. (2004), who included 3,398 fatally injured drivers. Importantly, testing positive for benzodiazepines was significantly associated with a 41% increase in accident responsibility (pooled OR 1.41; 95%CI 1.03-1.94).

Much of the literature examining the link between medicinal drug use and traffic accidents, has focused on the association between a whole class of drugs (e.g. benzodiazepines, opioids, antidepressants). This does not account for the potential differences between the individual drugs in these classes, and their variable impairment on driving ability. A recent study by Rudisill, Zhu, Kelley, Pilkerton, and Rudisill (2016) aimed to determine, through a systematic literature review, the risk of accidents associated with specific medications. The review included all studies that investigated individual preparations, and the associated odds or risk of a motor vehicle collision; this included cohort, case-control, and case-cross-over studies, and those using driving simulators. The review included 27 studies that spanned from 1992 to 2013, and of these, seven studies investigated nine different benzodiazepines. It was found that chlordiazepoxide (not available in Australia) and oxazepam were not associated with a significantly increased risk of collisions. However, flunitrazepam, flurazepam, lorazepam, temazepam, and triazolam were associated with a statistically significant increased risk of traffic collisions. Diazepam was associated with a significantly increased risk in four out of the five studies

investigating its effects. The review concluded that across all drug categories, there was variation within each class, meaning some specific preparations had a higher association with crash risk than others; therefore investigating medications as a class may at times obscure valid findings. Furthermore, not all medications that were associated with an increased risk of vehicle accidents, were correlated with decreased driving ability, and vice versa, suggesting that neither measure should be used a sole indication of a medication's impact on driver-impairment. However, some medications including; diazepam, flunitrazepam, flurazepam, lorazepam, temazepam, triazolam, and the Z-drugs - zopidem and zopiclone, were associated with both an increase in the risk of motor vehicle accidents and a decrease in driving ability, thus indicating these preparations are of particular importance to target for driver safety.

Epidemiological studies are limited in that they examine a select sample, and thus do not provide an indication of the usual prevalence of drugged driving. The regular detection of benzodiazepines in drivers involved in accidents points to the impairing effects of these drugs, however, a causal effect cannot be assumed. Experimental research provides an alternative method of examining the link between benzodiazepine use, and subsequent impairment.

Laboratory Tests

Experimental Tests

The impact of specific drugs on driving ability has often been explored using experimental laboratory testing. Laboratory testing, using tasks measuring specific abilities, such as reaction time or attention, allow the many abilities required for driving to be studied in a controlled environment. Kelly et al. (2004) reviewed the experimental research examining the association between benzodiazepine use and driving. Benzodiazepine use was associated with decreases in visual and speed perception, information processing, coordination, reaction time, memory, and attention. However, these effects were dose dependent, and there were not

consistent effects across the benzodiazepine types. The laboratory tests used in experimental research have often been chosen based on their ease of administration and sensitivity to drugs effects, rather than on face validity. These factors diminish the predictive ability of laboratory tests to on the road driving.

The release of drugged driving research guidelines by a panel of experts aimed to standardise future drug driving research (Walsh, Verstraete, Huestis, & Mørland, 2008). This panel identified that there are three core areas of behaviour most relevant to impaired driving. These domains include: (1) automative behaviour, or well-learned skills, including tracking, steering, and sustained attention; (2) control behaviours, such as motor performance, manoeuvres, divided attention, and perception; and (3) executive planning behaviours, for example, risk taking, impulsivity, information processing, and judgement.

As discussed in Chapter 2, a large quantity of laboratory research has established the cognitive deficits associated with benzodiazepine use, including in the three domains relevant to driving ability listed above. For example, a review by De Visser et al. (2002), examined acute benzodiazepine use in naïve users, and found deficits in attention, motor control, and executive function. Similarly in current and previous chronic benzodiazepine users impairment has been found in relevant areas of cognitive function including psychomotor speed, visuospatial skills, attention/concentration, motor control/performance, speed of processing, and problem solving (Barker et al., 2004a, 2004b). Whilst experimental research lacks validity for driving ability, the research clearly shows benzodiazepines impair cognitive functions important for safe driving.

Driving Simulators

Driving simulators are a method of laboratory testing assumed to have greater predictive ability to real life driving. Driving simulators range from simple systems, with basic components, such as a steering wheel, foot pedals, and computer screen, through to complex structures with realistic car bodies, and computer-generated

systems with authentic road scenarios. Common outcomes measured in simulator studies include: speed, steering, deviation from lateral position, reaction time, braking accuracy, driving errors, and vehicle collisions.

A study by Rapoport and Banina (2007) examined nine articles assessing the impact of psychotropic medications on computer simulated driving. Research was grouped according to when testing occurred in relation to drug ingestion; ≤ 2 hours post-ingestion, 2-5 hours post-ingestion, next morning effects, and during stable dosing of benzodiazepines. The time period up to two hours after dosing was most commonly studied. During this time period, higher doses of benzodiazepines (such as 2mg of lorazepam, or 15mg of diazepam) were associated with an increase in reaction time, and tracking errors. At 2-5 hours post dosing, some but not all studies found impairments in coordination, reaction time, and tracking ability, associated with benzodiazepine use. Reaction time was impaired the morning after 5mg of nitrazepam, but this impairment reduced after the third dose. Coordination was impaired for up to 14 days of dosing with 30mg of flurazepam. None of the studies focusing on 'morning after' effects examined longer-acting benzodiazepines, such as diazepam, or clonazepam, which may be more likely to cause lasting effects. Two of the studies reviewed examined the immediate impact of an acute dose in regular benzodiazepine users. Whilst one study found no effects, the second found that patients who had been using various benzodiazepines for several years, showed an increase in speed variation when tested one hour post dosing. The studies reviewed by Rapoport and Banina (2007) were difficult to compare due to methodological differences, and varying benzodiazepine doses. However, whilst there were some differences amongst studies, reaction time and tracking were quite consistently impaired by the use of benzodiazepines. A later meta-analytic study by the same lead author (Rapoport et al., 2009), reviewed epidemiological and experimental data examining benzodiazepines and driving. It was reported that many of the experimental driving studies were too heterogeneous to meta-analyse, and there were no consistent findings from the studies using driving simulators.

The ecological validity of driving simulators in assessing on-road driving ability is not yet established; research indicates a benzodiazepine deficit on simulated tasks, but inconsistency in results means clear conclusions are lacking.

Standard Deviation of Lateral Position and Road Based Driving Tests

The most accurate ecological validity lies in the domain of road-based driving tests. Standard deviation of lateral position (SDLP) is a commonly used on-the-road driving test, conducted during normal traffic, although this outcome measure is also sometimes used in simulator studies (Verster & Roth, 2011). The primary aim of the task is to remain at a steady lateral position on the road at a speed of 95km/hour; accuracy is measured by the degree of weaving of the vehicle from the path and variability of speed control.

A meta-analytic study by Roth, Eklov, Drake, and Verster (2014) examined 14 studies using on-road SDLP as the outcome measure. Four meta-analyses were completed examining; benzodiazepine hypnotics compared to Z-drugs, drug dosage, time of day of testing, and benzodiazepine half-life. The meta-analysis showed that when combining all hypnotic drugs used to treat insomnia, there was a significant impairment in morning driving performance, as measured by SDLP (p<0.001). Benzodiazepines impacted on performance to a greater extent than Z-drugs (p<0.001). When benzodiazepines were given at the recommended dosage of a night-time, SDLP was impaired in the morning (p<0.001), but not in the afternoon (p=0.089). Greater impairment occurred in morning drives compared to afternoon drives, at both single (d=0.27, p=0.001) and double doses (d=0.59, p=0.001). However, provision of a double dose caused greater impairment than a single dose, whether testing occurred in the morning (d=0.49, p=0.001), or the afternoon (d=0.33, p=0.001). As would be expected, there was an effect of benzodiazepine half-life on performance impairment. Short-acting hypnotics, with a half-life of less than six hours, did not affect performance the next morning. However both intermediate half-life (half-life of 6-12 hours; p<.0001) and long-acting (half-life of greater than 12 hours; p<.0001) hypnotics had an effect on SDLP the next morning.

This meta-analysis by Roth et al. (2014), replicates and extends upon the work from two earlier meta-analyses (Rapoport et al., 2009; Verster, Veldhuijzen, Patat, Olivier, & Volkerts, 2006). Results indicate benzodiazepine impairment is increased when time between intake and driving is short, with higher dosages, and with benzodiazepines with a longer half-life.

Most experimental driving studies are conducted using healthy individuals, however, this does not account for the underlying conditions for which benzodiazepines are prescribed. The ability to generalise from studies using healthy participants, to the effects on patients requiring benzodiazepine treatment remains limited. The Driving Under the Influence of Drugs, Alcohol, and Medicines (DRUID) group extended upon current studies by examining the effects of benzodiazepines in both healthy volunteers, and typical patient groups (those with anxiety or insomnia).

Touliou (2011) examined driving performance in benzodiazepine-treated anxiety patients (*n*=15), untreated anxiety patients (*n*=18), and a healthy control group (*n*=18). Participants were matched for age, gender, and driving experience. The anxious patients had a diagnosis of anxiety, and a score on the Hamilton Anxiety Rating Scale (Hamilton, 1959) of greater than, or equal to 2; which is indicative of anxiety of mild to moderate severity. Those in the treatment group, had been using alprazolam regularly for the past two months. Participants in the untreated group had not received any type of treatment in the last two months. Two driving tasks were completed using a driving simulator; the first task was a standardised test of SDLP, and the second was a car following scenario. In the car following scenario, a safe distance had to be maintained from a lead vehicle travelling at a steady speed (90km/hour); four instances of abrupt braking from the lead vehicle occurred randomly. The car following scenario yielded two measures; percentage of time driving spent within certain time-to-collision values, and braking reaction time. A standardised battery of attentional performance tasks was administered after the driving tasks (winTAPP: Zimmermann & Fimm, 1993). Driving measures, and

cognitive and subjective assessments were conducted at baseline and approximately one hour after administration of 0.5mg alprazolam. Alprazolam impaired performance in all three groups on SDLP. Results from the car following scenario regarding time-to-collision were not conclusive, but compared to anxious patients, the healthy controls were actually less likely to keep safe distances, indicative of poorer performance. Alprazolam affected braking reaction time in both treated and untreated anxiety patients. The treated group showed the greatest impairment in reaction time, suggesting that repeated alprazolam dosing, may have a greater effect on reaction time than once-off dosing. In the neuropsychological battery, alprazolam significantly affected alertness in the control group, however, no other significant differences were found. Effect sizes were not reported in the study. Overall the authors conclude that alprazolam significantly affects performance in anxious and control subjects.

Leufkens, Ramaekers, de Weerd, Riedel, and Vermeeren (2011) studied driving ability in elderly insomnia patients chronically using hypnotics (*n=22),* unmedicated elderly insomnia patients (*n*=20), and healthy age-matched controls (*n*=20). The age range of participants was 52-73 years, and insomnia patients met criteria for primary insomnia, according to the Diagnostic and Statistical Manual of Mental Disorders-IV (American Psychiatric Association, 2000). Use of hypnotics included both benzodiazepines, and zolpiclone, or zolpidem. The chronic hypnotic users had used a hypnotic at least four days a week, for at least three months. Average duration of hypnotic use was 7.7 years, with a mean frequency of use of 6.4 nights/week. Two driving tasks were used; a standardised highway driving test (O'Hanlon, 1984), with standard deviation of lateral position (SDLP) as the main outcome, and the car following test (Brookhuis, Waard, & Mulder, 1994; Ramaekers & O'Hanlon, 1994). As in the earlier simulator study (Touliou, 2011) the car following test required participants to drive behind another car, and follow its speed movements; however, in this study the test was completed on road, and average reaction time to the movement of the lead vehicle was the main outcome variable. The on-road tests were administered in the morning, 10-11 hours after

dosing. No significant differences between groups were found on the road driving tasks. Similarly, there were no differences on experimental tasks (verbal memory, divided attention, psychomotor vigilance, and inhibitory control), which were completed before and the morning after dosing, with the exception of working memory (digit span) where chronic hypnotic users performed significantly worse compared to controls. Overall results showed that driving performance in patients with insomnia is not impaired relative to controls, irrespective of the use of hypnotic medication. It is suggested that the relative simplicity of these tasks meant insomnia patients were able to compensate for performance deficits by increasing their effort. The authors state that the absence of a deficit associated with hypnotic use is likely to be an effect of tolerance.

Detection of Subjective Impairment

There is some evidence that benzodiazepines are associated with an impairment in the ability to monitor one's own performance, commonly known as metacognition. Practically, the inability to detect impairment in a task of high psychomotor demand, such as driving, could have severe consequences. It is also common to expect benzodiazepine users to determine their own impairment, for example before choosing to drive or operate machinery. There have been some attempts to examine the self-rated, subjective impact of benzodiazepines on driving ability.

Metacognition

Metacognition is commonly described as 'thinking about thinking' (Flavell, 1971, 1979). Whilst there is not complete agreement in the literature as to the specific nature of meta-cognition, most definitions seem to acknowledge the components of monitoring, and if necessary, changing one's performance (Georghiades, 2004). As there is an established benzodiazepine related cognitive impairment, capacity to detect this deficit is important, and inability to do so may have serious outcomes (Kleykamp, Griffiths, & Mintzer, 2010).

Research indicates benzodiazepines impair metacognitive abilities. One commonly studied area of metacognition is metamemory (Flavell, 1971); that is, knowledge and awareness of one's memory, particularly the capacity to self-assess and regulate (Mintzer, Kleykamp, & Griffiths, 2010). Impairment in metamemory has been noted in those administered lorazepam (Bacon et al., 1998; Izaute & Bacon, 2004; Massin-Krauss, Bacon, & Danion, 2002) and triazolam (Kleykamp et al., 2010; Mintzer et al., 2010). There is also evidence that benzodiazepines impair capacity to judge performance on other psychomotor tasks, such as the Digit Symbol Substitution Task (Mintzer & Griffiths, 2003), the circular lights task (Roache, Cherek, Bennett, Schenkler, & Cowan, 1993), and reduce awareness of internal states such as sedation (Mintzer & Griffiths, 2003; Weingartner et al., 1995). These studies are all undertaken in benzodiazepine-naïve healthy individuals, and thus findings cannot be extended to those who use benzodiazepines regularly.

Subjective Detection of Driving Impairment

Verster, Volkerts & Verbaten (2002) used a double-blind cross over design, to administer alprazolam (1mg) or placebo to benzodiazepine-naïve healthy individuals; both subjective and objective measures of performance were collected. As expected, alprazolam was associated with a significant deficit on measures of driving performance, including standard deviation of lateral position (p<.0001), and standard deviation of speed (p<.0001). This corresponded with the subjective ratings of participants; when compared to controls, participants given 1mg of alprazolam rated themselves as having significantly reduced driving quality (p<.0001), alertness (p<.0001) and mental activation (p<.0001), with increased mental effort required to drive (p<.0001). These findings suggest that participants in this study were able to detect impairment to their driving ability. However, six out of the 20 participants actually *fell asleep* whilst trying to complete the driving task, which indicates the degree of impairment experienced. The study used benzodiazepine-naïve participants only, and it is likely that in regular benzodiazepine users, impairment would be more subtle, and thus may not be so

readily detected. To date, to the author's knowledge, no studies comparing objective and subjective performance on ecological driving tasks in chronic benzodiazepine users exist.

Self-Report Survey Research

The Australian Drug Foundation completed an extensive online survey, and key stakeholder interviews to investigate the Australian community's experience and understanding of driving in conjunction with alcohol, licit and illicit drug use (Mallick, Johnston, Goren, & Kennedy, 2007). In this random internet sample (*n*=6,801) there was a higher representation of females, highly educated people, and drug use, compared to general population data. In the last 12 months, 12.6% of participants reported they had driven whilst over the 0.05% blood alcohol concentration (BAC). Comparatively 4% of all respondents reported that in the past 12 months, they had driven within 3 hours of benzodiazepine use. Likelihood of driving whilst acutely affected by a benzodiazepine increased proportionally with frequency of use.

Survey respondents were questioned about whether they detected any impairment on driving ability. Most respondents reported that there was no subjective change to their driving ability within three hours of using a benzodiazepine (67.4%). Approximately a quarter of participants perceived an impairment to driving ability, with 21.5% reporting that it was '*slightly worse*' and 4.1% reporting that it was '*a lot worse*'.

Attitudes and perceptions surrounding drink and drug-driving were also examined. It was found that 89.3% (*n*=6,331) of respondents considered that driving with a BAC of 0.05 or more, was '*very risky or dangerous*'. In comparison, 61.6% (*n*=4,188) thought that driving under the influence of benzodiazepines was '*very risky or dangerous'*. Driving under the influence of benzodiazepines was considered significantly more likely to be considered "*very risky"* by non-benzodiazepine users (64.2%, *n*=5,910) compared to benzodiazepine users (44.4%, *n*=891).

Overall findings from this study do not bode well for regular benzodiazepine users. Regular users were much more likely to drive within three hours of using a benzodiazepine, and less likely to consider that it was very risky to do so. Most of the group reported there was no change to their driving ability. Regular benzodiazepine users are a group that should be highly aware of the risks associated with benzodiazepines, and take relevant precautions. Data from the Australian Drug Foundation survey suggests that this is not the case.

Summary of Benzodiazepine and Driving Research

The evidence from epidemiological driving studies shows a strong association between benzodiazepine use and driving accidents. Benzodiazepine users are also more likely to be responsible for accidents they are involved in. Summarising laboratory testing, including simulator studies, has been difficult due to methodological issues, however, benzodiazepines do impair cognitive functions associated with driving. Evidence from on-the-road driving tests has high ecological validity and suggests significant driving impairment is associated with hypnotic benzodiazepines, including the morning after a night time dose. The extent to which benzodiazepine impairment can be self-detected remains unclear; it is possible that more subtle impairment may be missed. Self-report data suggests that even those who regularly use benzodiazepines may underestimate the risks involved with driving under the influence of benzodiazepines. The benzodiazepine and driving literature is difficult to summarise due to the broad range of methodology used and the variation inherent within the class of benzodiazepine drugs. However, deficits are quite consistently shown across many different studies, and the consequences associated with even a small deficit in driving ability are potentially fatal.

4 The Safety Incident Continuum

CHAPTER 4: THE SAFETY INCIDENT CONTINUUM

As has been illustrated, the importance of understanding the impact of benzodiazepine use on driving is significant given the potentially catastrophic impact of accidents. However, benzodiazepine users are likely to be susceptible to accidents across a range of daily activities. Whilst much of the previous research is dependent on data obtained in serious and often fatal accidents, a novel research approach by the Bristol Stress and Health studies, examined a range of incidents varying in severity (Smith, Johal, Wadsworth, Davey Smith, & Peters, 2000; Wadsworth, Moss, Simpson, & Smith, 2003, 2005; Wadsworth, Simpson, Moss, & Smith, 2003).

The incident types examined in the Bristol Stress and Health studies were measured both within and outside of the workplace and were as follows; (1) major accidents that required medical attention (2) minor injuries not requiring medical attention and (3) cognitive failures, or minor slips or lapses in normal cognitive function. An initial comprehensive study, the Bristol Stress and Health at Work Study (Smith, Johal, Wadsworth, Smith & Peters, 2000) examined factors related to stress at work via a mail out survey to 17,000 people in the Bristol Electoral register. This original study led to a series of follow up studies that have become more focused on specific substances and their impacts.

The most relevant of this group of studies was that by Wadsworth, Moss, Simpson, and Smith (2005) which focused on the impact of particular psychotropic medications. This study used a postal survey of a random community sample of 7,979 people in the Cardiff and Merthyr Tydfil electoral registers. Of this group, 58% (*n*=4,620) were employed, 58% (*n*=4,601) were female, and there was an average age of 45.6 years. Logistic regression was used to test for associations between medication use, demographic factors, and the outcome variables. Incidents were reported at the following rates; major accidents (11%), road accidents (2%), minor injuries (14% - quite or very frequent minor injuries), and cognitive failures (18% - quite or very frequent cognitive failures). Benzodiazepines were significantly

associated with non-work injuries (OR 4.43, 95%CI 1.89-10.38). There were also trends towards associations between benzodiazepines and general injuries (OR 2.17, 95%CI 0.89–5.32), work accidents (OR 1.36, 95%CI 0.13–14.58), and general accidents (OR 2.01, 95%CI 0.71–5.67). To clarify findings, comparisons were also made between participants who had low or high levels of other risk factors for each incident type (such as alcohol use or risk taking), and the presence or absence of a mental health condition. For those who had both a mental health condition and high levels of other risk factors, benzodiazepines significantly increased the risk of non-work injuries (OR 16.18, 95%CI 6.24-41.94) and cognitive failures (OR 18.09, 95%CI 6.17-53.04). A final set of analyses, focusing only on the groups with high other risks, suggested that there was an independent association between benzodiazepine use and injury risk (OR 3.06, 95%CI 1.32-7.10), over and beyond the effect associated with having a mental health condition (OR 1.67, 95%CI 1.28-2.17). There was also an interaction effect between mental health status, and benzodiazepine use on cognitive failures (OR 3.66, 95%CI 1.26-10.66), which had a greater effect than the impact of mental health problems alone (OR 2.14, 95%CI 1.69-2.70). The findings of the Wadsworth study indicate a detrimental effect on the safety of benzodiazepine users, but this did not occur across all incident types. To our knowledge, no other studies have investigated the association between psychotropic medication use, and accidents, injuries and cognitive failures within the one set of analyses. The main effects of benzodiazepines on each of these incident types will be reviewed below.

Major Accidents

Major accidents, as defined by Wadsworth, Moss, et al. (2003), are those accidents that are high enough in severity to require medical attention. Major accidents are the outcome most commonly measured in research, as inherent in their nature, they require presentation to medical services, and thus can be readily tracked. As traffic accidents have already been reviewed in an earlier section, only non-traffic accidents will be covered here.

An epidemiological study by Kurzthaler et al. (2005), examined the types of incidents that led to people under the influence of alcohol or benzodiazepines presenting to an emergency room. The sample was collected over a one year period and involved 1,611 people presenting to the emergency department in Innsbruck, Austria; 19.5% (*n*=314) of people tested positive for alcohol, 5.2% (*n*=85) for benzodiazepines, and 1.4% (*n*=23) were positive for both substances. In injured people, benzodiazepines were significantly more common in violence-related injuries (19.6%) than any other accident type; this was also the most common injury type for alcohol and alcohol/benzodiazepines in combination also. Following violence related injuries, rates of benzodiazepine detection occurred the next most commonly in traffic incidents (7.1%), followed by falls (5.5%), sport injuries (3.8%) and work place accidents (2.3%). Whilst this study only indicates correlation not causality, results do give some indication of the types of accidents associated with benzodiazepine use.

Palmer, Harris, and Coggon (2008) undertook a systematic literature review of chronic health conditions and related medications, and workplace accident risk. A total of 38 relevant papers from 1966 to 2006 were reviewed. Criteria for exposure variables and outcomes were too varied to warrant a meta-analysis. Across the papers reviewed, the association between anxiolytics, hypnotics, or sedatives, and workplace accidents was mixed, though some significant positive associations were found. Voaklander et al. (2006) found that use of anxiolytics/hypnotics/sedatives in the past 30 days was associated with a three-fold increase in the risk of work-related accidents in elderly farmers (OR 3.01, 95%CI 1.39-6.52). The studies of Wadsworth, Moss, et al. (2003) and the earlier described study of Wadsworth et al. (2005) used a similar methodology. The 2003 study was a preliminary investigation of the association between ‘sleeping tablets’ and anti-depressants, and accidents, injuries and cognitive failures. In a general postal survey of 3,111 individuals, there were significant associations between benzodiazepine use and accidents at work (adjusted OR=2.82, 95%CI 0.84-9.44) and outside of work (adjusted OR 1.75, 95%CI 0.95-3.24). The limitation inherent in this review by Palmer et al. (2008) is that there

is no indication that the use of benzodiazepines coincided with the accident experience.

Psychotropic medications are commonly linked with increased rates of falls, particularly in the elderly. Bloch et al. (2011) undertook a systematic literature review and meta-analysis of psychotropic medications in people aged 60 and above, and their experience of everyday falls. 177 relevant studies published between 1996 and 2007 were reviewed (*n*=20,576). There were associations between psychotropic medication use and falls (OR 1.78, 95%CI 1.57-2.01) and benzodiazepine use and falls (OR 1.39, 95%CI 1.24-1.54). The overall study findings supported that of an earlier meta-analysis (Woolcott et al., 2009). The authors conclude that despite strong evidence of the relationship between psychotropic medications and falls, there has been little change in prescribing behaviour.

Minor Injuries

For the purpose of this thesis 'minor injuries' are considered to be minor non-venous cuts and scrapes that do not require medical attention (Wadsworth, Simpson, et al., 2003). The extent and cost of major accidents is commonly captured by workplace reporting systems, and medical services; however, there is a relative scarcity of research examining minor injuries (Simpson, Wadsworth, Moss, & Smith, 2005). Even in the general population, there is little information about rates of minor injuries. For example, Safe Work Australia, responsible for work health and safety, only publishes information about serious claims resulting in a worker's compensation case. Despite this, minor injuries are important in their own right, and can have a serious impact on well-being.

Wadsworth, Moss, et al. (2003) found initial associations between sleeping tablet use and minor injuries both at and outside of work, but these were explained by other demographic and lifestyle variables in a multivariate analysis. In a larger sample (Wadsworth et al., 2005), benzodiazepines were significantly associated with non-work injuries (OR 4.43, 95%CI 1.89-10.38), and for those with other risk

factors and a mental health condition, the association between benzodiazepines and non-work injuries increased considerably (OR 16.18, 95%CI 6.24-41.94)

Cognitive Failures

Wadsworth, Simpson, et al. (2003) defined cognitive failures as problems of memory (e.g. forgetting where you put things), attention (e.g. failures of concentration), or action (e.g. making an unintended action). Cognitive failure is a term that has been broadly used to encompass a range of errors, and represents a slip in normal functioning, rather than a failure occurring due to lack of ability (Broadbent, Cooper, Fitzgerald, & Parkes, 1982). For example, forgetting to complete a routine task at work that would normally be handled efficiently would be considered a cognitive failure, compared to being unable to complete a task due to lack of necessary skills (failure of ability). Whilst everyday cognitive failures for the most part have a relatively benign, albeit frustrating outcome, in some instances they may result in more serious incidents, for example forgetting to turn a heater off, or crossing an intersection at a red light. Research has established some serious behavioural consequences arising from cognitive failures, including absent-minded shop lifting (Reason & Lucas, 1984), car accidents (Larson & Merritt, 1991), and other accidents (Larson, Alderton, Neideffer, & Underhill, 1997).

Prospective memory and retrospective memory are processes prone to cognitive failures. Retrospective memory is involved with remembering previously learned information, and is historically a well-studied concept; many standard recall and recognition tasks are dependent on retrospective memory (Crawford, Henry, Ward, & Blake, 2006). Prospective memory frequently described as ‘remembering to remember’, is involved with memory for future intentions. Whilst prospective memory has only more recently received attention, it is vital for making future actions and plans, and is a critical feature for the completion of many everyday tasks (Ellis & Kvavilashvili, 2000). Whilst prospective memory and retrospective memory are distinct concepts, they interact in the day-to-day memory required to live independently (Crawford & Smith, 2003). For example the simple task of

needing to stop at a pharmacy and pick up medication, requires both prospective memory (remembering to stop) and retrospective memory (remembering what you need to buy).

The impact of benzodiazepines on memory is highly researched; a general detrimental effect occurs, but the many types of memory processes are differentially affected by benzodiazepines (Barker et al., 2003; Rich, Svoboda, & Brown, 2006). The varying models of memory that are common in the literature make summarising the research difficult. A review by Buffett-Jerrott and Stewart (2002), indicates there are minimal benzodiazepine induced effects on short-term memory, with a more significant deficit in long-term memory. Within the construct of long-term memory, benzodiazepine use appears to impair explicit memory (conscious effortful memory, and participant is aware that testing is occurring), and have a time and dose dependent effect on implicit memory (outside of conscious awareness, and participant is not aware that testing will occur). Buffett-Jerrott and Stewart (2002) suggest that future memory studies need to focus on measures more applicable to everyday memory.

The effect of benzodiazepines on retrospective memory has been well studied using recall and recognition tasks. Whilst benzodiazepines impair retrospective memory, this impairment only occurs for information learned after drug administration, which is often referred to as anterograde memory/amnesia (Barker et al., 2003). Benzodiazepines seem to impair the acquisition process of learning new information, by disrupting the ability to form new associations between events, and impairing the consolidation phase of new memories (Beracochea, 2006).

Despite the enormous quantity of literature examining benzodiazepines and memory, the research focusing on prospective memory is scarce. An exploratory study by Rich et al. (2006), examined the effect of a single dose of diazepam compared to placebo, on retrospective and prospective memory, sustained attention, and subjective arousal. In this exploratory study, one naturalistic prospective memory task was hidden amongst several retrospective memory tasks.

The prospective memory task required participants, upon receiving a verbal cue, to request a personal belonging taken from them earlier. Retrospective memory tasks included word recall and digit span tasks. Results found expected deficits in retrospective memory tasks for the diazepam users. In the prospective memory tasks the diazepam group required more reminders to request their hidden belonging than the placebo group (*d*=0.65). Despite associations between prospective memory, retrospective memory, and arousal measures, the authors conclude that there are likely independent effects of diazepam on prospective memory. However, only one prospective memory task was used in this study, so generalisability cannot be assumed. At the time of this study, the authors were the first to examine the effect of benzodiazepines on prospective memory, and since that time there seems to be no substantial published studies looking at this area.

Summary

Experience of safety incidents can be understood as a continuum of outcome severity. Benzodiazepine use has been shown to be associated with three incident types: major accidents, minor injuries, and cognitive failures. Whilst major accidents are the incident with the most serious outcome, each of these incident types can impact on a person's wellbeing. Understanding how chronic benzodiazepine use uniquely effects each of these incident types will help to clarify the full range of consequences of benzodiazepine use.

5 Thesis Introduction and Rationale

CHAPTER 5: THESIS INTRODUCTION AND RATIONALE

Theoretical Summary and Rationale

Benzodiazepines are a group of commonly prescribed medications that are used for a wide variety of reasons, such as preoperative anaesthesia, anxiety, sleep disorders, alcohol withdrawal, and epilepsy. As a class of drugs, benzodiazepines vary considerably in their potency, and the speed at which they are metabolised and eliminated from the body. The considerable variation in half-life and potency is an important consideration in the selection of which benzodiazepine will be chosen to treat a condition. However, it is also one of the main difficulties in reconciling benzodiazepine research; dose and type of benzodiazepine studied varies greatly, as do their psychomotor effects. The conversion to a diazepam equivalent dose in the current thesis, allows comparisons to be made across the varying types and dosages of benzodiazepines.

It is well established that during short-term use of benzodiazepines, there are a range of side-effects with deleterious effects on safety, including sedation, confusion, dizziness, and memory problems. For these reasons, patients are commonly urged to use caution when first taking benzodiazepines, especially when undertaking cognitively demanding activities, such as driving. However, the ongoing risk associated with longer-term benzodiazepine use remains less researched. Meta-analyses have found ongoing benzodiazepine use negatively effects a range of cognitive areas, in both current users (Barker et al., 2004a), and those who have ceased use (Barker et al., 2004b). Making clear recommendations about long-term use of benzodiazepines is also complicated by the differential development of tolerance to particular aspects of these medications (Vinkers & Olivier, 2012). The relatively quick development of tolerance to many of the therapeutic effects, in combination with the potential for dependence, has led to clinical recommendations that suggest benzodiazepines are used at the lowest dose, for the shortest time period possible (National Health and Medical Research Council, 1991; Royal Australian College of General Practitioners, 2000).

Despite recommendations limiting the use of benzodiazepines being in place for over 35 years, there is evidence that use remains widespread and often long-term. Whilst overall benzodiazepine prescription appears to have plateaued (Stephenson et al., 2013), over 7 million benzodiazepine scripts are written in Australia each year and research suggests that quantity per script may be increasing (Islam et al., 2013). Long-term use has also been shown to regularly occur, although in the past 5-10 years this has not been re-reviewed.

A review of the benzodiazepine literature reveals the populations studied are usually young, healthy, benzodiazepine-naïve males. This is a group that is clearly at odds with the average benzodiazepine user who is more likely to be an older, anxious female, using for an extended period of time (Neutel, 2005; Nordfjaern et al., 2014; Olfson et al., 2015). This thesis aims to move away from the typical benzodiazepine research that examines brief dosing regimens in healthy individuals. Instead, the aim is to examine benzodiazepine use as it naturally arises in the Australian community; with varying levels of chronicity, and occurring amongst a range of other confounding variables.

A large body of the research to date has examined the relationship between benzodiazepines and driving safety. Driving is an everyday task with a large psychomotor requirement, and any adverse effects caused by benzodiazepines could have catastrophic consequences. The risk of driving after using benzodiazepines has been equated to a similar level of risk as driving with a blood alcohol concentration of 0.05-0.08% (Hels et al., 2011). Much of the research examining the association between benzodiazepines, and traffic and other accidents, has relied on data obtained from medical services. Conversely, research by Wadsworth and colleagues (Simpson et al., 2005; Wadsworth, Moss, et al., 2003; Wadsworth et al., 2005) recognised that there is more often a continuum of accident severity, including; cognitive slips or errors, minor injuries, and more major accidents requiring medical attention. This research aims to extend that completed

in the United Kingdom to an Australian context, by examining a full range of incident severities.

It is also important to recognise that whilst benzodiazepines are commonly prescribed and used appropriately, they are also frequently used illicitly for intoxication purposes (Darke, Topp, & Ross, 2002; Fry & Bruno, 2002). People who inject drugs (PWID), commonly use benzodiazepines to reduce the symptoms of opiate withdrawal, for their sedative and hypnotic effects, or for the synergistic effects when combined with other depressants. PWID are known to be a risk-taking population (Stafford & Burns, 2014), with high mortality (Mathers et al., 2013). It is important to consider how benzodiazepines independently contribute to safety in PWID, beyond the impact of other drug use and other risk-increasing factors.

Reviewing the research to date guides the direction for the current studies. Firstly, in 2014 there were almost 6.5 million scripts dispensed for a population of 24.5 million (Department of Health, 2015), which demonstrates the pervasiveness of the use of benzodiazepines and the importance in understanding how benzodiazepine use effects the everyday safety of consumers. To fully understand safety consequences, it is necessary to focus not just on serious accidents, but to also examine the more minor incidents that may occur. Secondly, research must focus on the chronicity of benzodiazepine use as it occurs in the community, rather than focusing on naïve users, or only brief benzodiazepine dosing regimens. Finally, the impact of benzodiazepines is complicated by many lifestyle factors, such as other drug use, health factors, and the attitudes and beliefs of the consumer; research must examine benzodiazepines within the context of these other factors. Understanding the experiences and views of current benzodiazepine users will help to inform quantitative research.

Aim & Research Questions

The aim of this research is to examine the objective and subjective associations between ongoing benzodiazepine use and safety. The research aims to explore the relationship between benzodiazepine use, and a continuum of different incident severities, in both a general, and high risk (people who inject drugs) population sample. Controlling for demographic, health, and drug use factors will allow the unique effects of benzodiazepines to be determined. This research also aims to conduct a qualitative exploration of the experiences and beliefs of current benzodiazepine users, in relation to their well-being and safety, which will complement the objective data obtained.

Research questions 1.1 and 1.2: The Effect of Benzodiazepine use on Safety:

- What are the associations between ongoing benzodiazepine use and various incident types including;
    I. Major accidents – non-traffic related accidents requiring medical attention
    II. Minor Injuries – non-traffic related, non-venous injuries that did not require medical attention
    III. Cognitive Failures – prospective or retrospective memory problems
    IV. Traffic accidents – in which damage to person or property occurred
    V. Close calls – where a traffic accident was narrowly avoided
- Is benzodiazepine use associated with each of the incident types listed above in the same way, or are some incident types more susceptible to benzodiazepine use?

Research Question 2.1 and 2.2: Dose, duration and frequency of benzodiazepine use:

- What association does chronicity of benzodiazepine use have with each incident type?
- Is experience of incidents associated more strongly with dosage, or pattern (duration and frequency) of benzodiazepine use?

Research Question 3.1 and 3.2: Benzodiazepine use in people who inject drugs (PWID):

- Following on from *research questions 1.1 and 1.2*, in PWID, what are the associations between benzodiazepine use, and major accidents, minor injuries and cognitive failures?
- What other alcohol or drug use is associated with major accidents, minor injuries, and cognitive failures in PWID?

Research Question 4.1, 4.2 and 4.3: Subjective experience of benzodiazepine side-effects:

- What do regular consumers know about the side-effects of benzodiazepines?
- From what sources is information about side-effects obtained?
- What side-effects do consumers detect and does this change over time?

Research Question 5.1, 5.2 and 5.3: Perception of impairment to driving ability:

- Do benzodiazepine consumers detect any impairment to their driving ability when first using benzodiazepines?
- Does any impairment change over time as benzodiazepine use progresses?
- Do people take any precautions regarding benzodiazepine use and driving?

Research Question 6: General Worries and Concerns:

- What are the general worries and concerns that regular benzodiazepine consumers experience (related to their benzodiazepine use)

Research Design

With the aim of answering these research questions, data were obtained from two surveys:

Survey 1: The '*Benzodiazepine, Health, and Driving*' survey was constructed with the specific aim of providing data for this research. The survey, shown in the appendix, was an online survey, examining a general population sample, recruited through a range of advertising sources. Participants reported their lifetime benzodiazepine use and their experience of varying types of safety incidents over the past 12 months. Data was also collected for a range of potentially confounding factors such as demographic factors, other drug use, and mental and physical health status. Data obtained from this study is aimed at answering *research questions 1, 2, 4, 5, and 6.*

Survey 2: With the aim of answering *research question 3*, data were taken from relevant sections of the Illicit Drug Reporting System (IDRS), an Australian drug monitoring system. This well-known, annual survey recruits individuals over 18 years of age, who have injected an illicit drug in the preceding six months. Data was taken from the 2009 and 2010 completions of the IDRS, with 2010 data being excluded from those who had completed the survey in both years.

Organisation

Each of the three main research areas investigated in this thesis are discussed in the following three chapters.

Chapter 6 examines the self-reported safety experience of chronic benzodiazepine users. The association between varying levels of benzodiazepine chronicity and a range of incident types was explored *(Research Question 1 and 2).* The survey

approach used in this study allowed benzodiazepine use to be explored within the context of other relevant variables.

Chapter 7 retains the same area of focus as *Chapter 6*, but a more specific population group was studied; people who inject drugs (PWID). The aim of this study was to understand whether benzodiazepines uniquely contributed to risk of safety incidents in people who inject drugs *(Research Question 3).*

Chapter 8 examines the personal experiences of regular benzodiazepine users. Specifically, the study focused on the safety and wellbeing of the respondents, and their experiences of benzodiazepine use *(Research Question 4, 5, and 6).*

Chapter 9 comprises a general discussion and integration of the thesis. The chapter aims to explore how the subjective experiences of chronic benzodiazepine users informs, and corresponds with the more objective measures of incident experience. Suggestions are made as to how these findings can guide clinical practice.

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6 Accidents, Injuries, and Cognitive Failures in Chronic Benzodiazepine Users

CHAPTER 6: ACCIDENTS, INJURIES, AND COGNITIVE FAILURES IN CHRONIC BENZODIAZEPINE USERS

Preface

This chapter investigates chronic benzodiazepine use in the general population (*Study 1*). The focus of this chapter is to examine the association between safety incidents *(Research Question 1)* and benzodiazepine use of varying chronicity *(Research Question 2)*. The association between benzodiazepine use and more serious accidents is well studied. However, *Study 1 and 2* aimed to extend on research by Wadsworth and colleagues, by examining a full range of incidents, including cognitive failures, minor injuries, and accidents requiring medical attention. Data for the current chapter and C*hapter 8* was obtained through the use of an online survey. By using a sample from the Australian general population the impact of regular benzodiazepine use can be explored as it naturally occurs, rather than a carefully crafted experimental drug regimen. Unlike much of the research that examines healthy, benzodiazepine-naïve individuals, this allowed benzodiazepines to be studied in the context of other confounding variables such as health factors and drug-use.

ABSTRACT

Background

Benzodiazepines are recommended to be used for short-term treatment, usually for less than four weeks, due to the high risk of dependence and psychomotor effects. Despite this, there is evidence that within Australia, benzodiazepines are still prescribed more frequently than clinical guidelines would recommend. The chronic use of benzodiazepines is relatively less studied compared to the acute effects. This paper aimed to investigate the associations between *chronic* benzodiazepine use and safety incidents. A continuum of incident types was examined including; major accidents, minor injuries, and cognitive failures.

Method

Data was collected from 129 participants using an online survey that ran from 2013-2015. Participants were required to; be over 18 years of age, be an Australian resident, have used a benzodiazepine during the last 12 months, and have a current driver's license. Data was collected for the safety incident outcome variables, and other confounding factors.

Results

From the reported benzodiazepine use, three categories of benzodiazepine chronicity were established; short-term (length of use ≤ year; daily/occasional frequency), intermittent (length of use > year; occasional frequency) and chronic (length of use > year; daily frequency). Even in the short-term user group, use spanned on average almost six months – far beyond the recommended four-week period. Compared to the general population, rates of accidents were elevated in the sample. Intermittent users were at significantly decreased risk of general accidents (Univariate OR= 0.32, 95%CI 0.11-0.94, p=0.037), retrospective memory problems (Univariate OR=0.16, 95%CI 0.06-0.71, p=0.007), and prospective memory problems

(Univariate OR= 0.21, 95%CI 0.04-0.60, *p*=0.012), compared to chronic, daily, consumers.

Conclusion

This study of benzodiazepine consumers in the general community identified chronic and risky patterns of benzodiazepine use. Chronic users were at a higher risk of safety incidents, suggesting that tolerance to potentially dangerous side-effects does not occur. Benzodiazepine use that is chronic in frequency, duration, and dosage must remain a target for harm minimisation.

INTRODUCTION

Benzodiazepines are a diverse class of drugs employed to treat many conditions, through their hypnotic, anxiolytic, anticonvulsive, and muscle relaxant properties. The short-term efficacy of benzodiazepines has led to their escalating use worldwide. However, concerns about the consequences associated with continued use have generated research and debate. The recent pharmaceutical rescheduling of alprazolam in Australia, to require tighter restrictions on prescription, storage, and dispensing, points to the magnitude of this issue (Department of Health, 2013).

The effect of initial benzodiazepine use is well-established; with new users cautioned about psychomotor effects including drowsiness, decreased concentration, and motor impairment (Barker, Jackson, Greenwood, & Crowe, 2003). The risk of side-effects, addictive potential, and reduced efficacy with sustained use (Ashton, 1995; Voshaar, Couvee, Van Balkom, Mulder, & Zitman, 2006) has led to clinical guidelines that recommend benzodiazepines are used at the *lowest dose*, and for *the shortest time period possible* (National Health and Medical Research Council, 1991; Royal Australian College of General Practitioners, 2000). Recommended use is suggested to be no more than four weeks, and longer term therapy is endorsed only when there is a clear rationale, when use is intermittent, and when other first line treatments have not been successful (Royal Australian College of General Practitioners, 2015b).

Despite these restrictive recommendations, there is evidence that clinical practice differs. Examination of benzodiazepine dispensing in Australia from 1992-2011 found that nearly 7 million benzodiazepine prescriptions were given through PBS, RPBS, and private scripts each year (Islam, Conigrave, Day, Nguyen, & Haber, 2013). Whilst more recently there has been some plateau in script numbers, usage remains at a high level and a shift towards private scripts is associated with the quantity per script increasing (Islam et al., 2013). Additionally, duration of use is often longer than clinically recommended. For example, an Australian longitudinal study of 337 people aged over 75 years, examined participants at 3- and 4.5- years post intake

and found 16.6% of participants were using benzodiazepines at all three time points (Jorm, Grayson, Creasey, Waite, & Broe, 2000). Similarly, in 2006 a study of Tasmanian residential aged care facilities found that 62.4% of those reviewed (*n*=1,307) were also taking the same dose of benzodiazepines 12 months later (Westbury, Beld, Jackson, & Peterson, 2010). Rates of benzodiazepine use are increased because benzodiazepines are used not just for prescribed purposes, but are commonly diverted and used for intoxication (Australian Institute of Health and Welfare, 2011). In addition to this, it is also suggested "Australia is likely to have a large, but relatively hidden, population who unintentionally misuse benzodiazepines" (Royal Australian College of General Practitioners, 2015b: p.6).

It is widely assumed that long-term users of medications become less sensitive to the effects of that medication, due to the development of tolerance. However, tolerance to benzodiazepines does not occur in a straightforward manner (Vinkers & Olivier, 2012). Tolerance to the hypnotic and anti-convulsant effects occurs quickly, whereas tolerance to the anxiolytic and amnestic effects occurs more slowly, if at all (Vinkers & Olivier, 2012). This means that research findings from studies of acute or brief dosing, cannot be extrapolated to chronic users. It cannot be assumed that regular benzodiazepine users are no longer at risk of cognitive and psychomotor impairment.

Laboratory research has established there are cognitive deficits associated with long-term benzodiazepine use. A meta-analysis by Barker and colleagues (Barker, Greenwood, Jackson, & Crowe, 2004a) examined 13 studies that investigated chronic benzodiazepine users. Benzodiazepine use varied between 1-34 years, with a mean duration of 9.9 years usage. In 11 out of the 13 studies a control group was used, including people classified as; non-anxious, anxious, and previous benzodiazepine users. Twelve cognitive domains were studied; sensory processing, psychomotor speed, nonverbal memory, visuospatial, attention/concentration, speed of processing, general intelligence, working memory, problem-solving, verbal memory, motor control/performance and verbal reasoning. Current benzodiazepine

users were significantly impaired across all domains, compared to controls, with moderate to large effect sizes found (mean weighted effect size =-0.74, *SD*=0.25), and no 95% confidence interval spanned zero, suggesting the effects were statistically significant.

A large body of benzodiazepine research has focused on driving ability. Given the known psychomotor impairment associated with benzodiazepines, including decreased attention, coordination, memory and wakefulness (Barker et al., 2003), it is important to understand the impact of benzodiazepines on this common, but high risk activity. Recent Australian guidelines conclude the literature on benzodiazepines and driving suggests a dose-proportionate risk of accidents, even with longer-term, stable dosing (Royal Australian College of General Practitioners, 2015b). A recent meta-analysis found that benzodiazepine users were 60-80% more likely to be involved in traffic accidents (for case-control studies: 59%, pooled OR 1.59; 95%CI 1.10-2.31, and for cohort studies: 81% pooled incidence rate ratio 1.81; 95%CI 1.35-2.43), and importantly were 40% more likely to be 'responsible' for the accident (pooled OR 1.41; 95%CI 1.03, 1.94) (Dassanayake, Michie, Carter, & Jones, 2011). The relative risk of driving after using benzodiazepines has been equated to driving with a blood alcohol concentration of 0.05-0.08% (Hels et al., 2011).

Limitations with the Australian driving research to date is that much of it is laboratory based and thus lacks face-validity, or it examines the effects of once-off, or short-term benzodiazepine use. Furthermore, accident rates are commonly obtained from those apprehended for impaired driving, or presenting to medical services. As such, it is likely that lower level driving incidents are not accurately identified. These 'near misses', may include occasions of late braking, missing traffic signals, poorly timed lane changes and so on. There is a significant gap in the research looking at the association between traffic incidents of different severities, in long-term, Australian benzodiazepine users.

Whilst driving is one task of particularly high cognitive demand, benzodiazepine users are likely to be at an increased risk of accidents in many aspects of their lives.

Research by Wadsworth, Moss, Simpson, and Smith (2005) explored the impact of psychotropic medication use on incidents of varying severities, using a randomised general population postal survey in the United Kingdom (*n*=7979). This group examined the safety of psychotropic medication users across a range of incident types both at, and outside of work, including; cognitive failures (everyday cognitive slips or errors), minor injuries not requiring medical attention, and major accidents requiring medical attention. Significant associations were found between benzodiazepine use and non-work injuries, with benzodiazepine users almost four and a half times more likely to experience a non-work injury, than non-medication users (OR 4.43, 95%CI 1.89-10.38). To further clarify findings, participants were classified by mental health status, and according to low or high presence of other risk factors associated with the incident type, such as physical health, age, and risk-taking. In the presence of high risk factors, and a mental health condition, benzodiazepine use markedly increased the risk of non-work injuries (OR 16.18, 95%CI 6.24-41.94) and cognitive failures (OR 18.09, 95%CI 6.17-53.04), compared to those not using any medication. The increased danger for those with high levels of other risk factors points to the importance of examining benzodiazepine use in the context of other lifestyle factors.

Lower severity incidents, such as minor injuries and cognitive failures, are less frequently studied, firstly because their outcomes are usually less critical, and secondly because they are not naturally recorded through presentation to medical services. However, repeated lower severity incidents are likely to have their own effect on a person's well-being. It is also suggested that an elevated number of cognitive failures may compound risk of higher severity incidents, depending on the context in which they occur (Simpson, Wadsworth, Moss, & Smith, 2005). For example, a cognitive failure whilst driving, such as a lapse in concentration, could lead to a much more serious accident. Examining a full range of incidents, allows a thorough investigation of the effects of benzodiazepines on safety.

Cognitive failures are defined as problems of memory, attention, or action; these failures are commonly occurring and usually benign, but can have serious consequences (Wallace, Kass, & Stanny, 2002). Cognitive failures normally reflect an error in typical functioning rather than a lack of ability (Wallace et al., 2002). Prospective memory errors (forgetting to perform a future event) and retrospective memory errors (forgetting previously learned information) are examples of cognitive failures. Retrospective and prospective memories interact in the everyday memory required to live independently (Crawford & Smith, 2003). For example, remembering to stop and buy groceries requires both prospective memory (remembering to stop) and retrospective memory (recalling what you needed to buy). A general detrimental effect of benzodiazepines on memory is well-established, but distinct memory processes are differentially affected by benzodiazepines (Barker et al., 2003; Rich, Svoboda, & Brown, 2006). Experimental studies are indicative of a dose- and time- dependent effect of acute use of benzodiazepines on retrospective and prospective memory (Barker et al., 2003; Rich et al., 2006). However, there have been few studies examining the relationship between chronic benzodiazepine use, and retrospective and prospective memory failures.

Despite the extent of the benzodiazepine literature, gaps remain in the research to date. Many studies look at young, healthy, benzodiazepine-naïve, males - a group far removed from the typical benzodiazepine using population. The current study examined a sample of Australian benzodiazepine consumers, with varying chronicity of use. The study design allowed the influence of other lifestyle characteristics, such as health, medications, and demographic factors to be examined. The aim of this study was to examine the impact of chronic benzodiazepine use on a range of incident types including cognitive failures, minor injuries, and major accidents, in both driving and general contexts.

METHOD

Participants and Procedure

Data was collected through an online survey run from 2013-2015. The survey was marketed to Australian residents through advertising in doctor's surgeries, pharmacies, hospitals, and targeted social media. On completion of the survey, participants could choose to enter a prize pool for 1 of 3 $500 vouchers. 251 participants initiated the survey with 122 participants excluded from the analysis (leaving a total pool of 129 participants). Unfortunately, high numbers of participants provided no data relevant to the outcome variables, before exiting the survey, and thus had to be excluded from the analysis. Initial survey questions excluded those who were under 18 years of age, had not used a benzodiazepine in the last 12 months, or who did not agree to informed consent statements. The survey took approximately 30 minutes to complete, and non-relevant sections were excluded based on initial screening questions, reducing the total time required. Major survey sections included questions on: demographic information, benzodiazepine use, licence and driving, road accidents, perceptions of benzodiazepines, general accidents, memory, alcohol and other drug use, health, and other medication use (antidepressants, antipsychotics, painkillers, and other psychotropic medications). Ethical approval was granted by the Tasmanian Social Sciences Human Research Ethics Committee (approval number H0012343).

Outcome variables

Data was collected on a range of different incident severities; outcome variables and relevant survey questions are listed below (Table 1).

For traffic accidents, traffic close calls, and general accidents, the number of incidents experienced was recorded, and for each incident type, those reporting more than one incident were compared with those who reported none. Minor injuries were rated on a five-point frequency scale, with frequency of occurrence

ranging from 'not at all' through to 'very frequently'. Those rating their experience of minor injuries as 'quite' or 'very' frequent, were classified as frequently experiencing minor injuries, and were compared to those who reported experiencing them less frequently. These questions were taken from the survey used by Wadsworth and colleagues (Wadsworth et al., 2005; Smith, Johal, Wadsworth, Davey Smith, & Peters, 2000).

Table 1*. Analysis Outcome Variables and associated Survey Question*

Outcome variable	Survey Question(s)
Driving Accident: Ever	When you have been driving, how many road crashes have you ever been involved in?
Driving Accident: 12 months	In the last 12 months when you have been driving, how many road crashes have you had?
Driving Close Call: 12 months	In the last 12 months when you have been driving, how many close calls have you had (i.e. incidents that almost resulted in a crash but did not)?
General Accident: 12 months	Thinking about the last 12 months, how many accidents have you had that required medical attention from someone else (e.g. a first aider, GP, nurse, or hospital doctor)?
Minor Injury: 12 months	In the last 12 months how frequently have you had minor injuries (e.g. cuts and bruises) that did not require medical attention from anyone else?
Minor Injury: 1 month	In the last month how frequently have you had minor injuries (e.g. cuts and bruises) that did not require medical attention from anyone else?
Cognitive Failures	Prospective Retrospective Memory Questionnaire (Crawford & Smith, 2003)

Day-to-day cognitive failures were assessed using the Prospective and Retrospective Memory Questionnaire (PRMQ: Smith, Della Sala, Logie, & Maylor, 2000). The PRMQ has 16 items, split equally between those measuring prospective memory problems (e.g., *Do you decide to do something in a few minutes time and then forget to do it?*) and retrospective memory problems (e.g., *Do you forget something that you were told a few minutes before?*). Problems experienced in the last 6 months are rated on a 5-point scale ranging from 'never', to 'very often'. Higher

scores are indicative of memory problems. Confirmatory Factor Analysis of the PRMQ items indicates best fit for a three-factor model, with a general memory factor and two orthogonal factors; prospective and retrospective memory (Crawford & Smith, 2003; Rönnlund, Mäntylä, & Nilsson, 2008). Crawford and Smith (2003) provide normative data based on a general adult UK population (*m*=38.88, *SD*=9.15), and using Cronbach's alpha there is strong internal consistency for the PRMQ (prospective scale α=0.84, retrospective scale α=0.80 and total scale α=0.89). Problem scores were defined as a score more than one standard deviation above the UK general population mean (prospective memory, scores ≥25.09; retrospective memory, scores ≥23.67).

Measures

The predictor variables were chosen due to their known association with decreased safety and/or their potentially confounding nature (Table 2). Each of these variables were used as a categorical variable, with cut-off scores chosen to denote 'at risk' versus 'low-risk' groups. This then allowed for the demarcation of a level at which an incident variable occurred, rather than simply providing information on the relationships between variables, as would have happened if the variables were treated in a continuous manner. All variables were binary with the exception of education level and benzodiazepine chronicity which had three levels to allow for greater clarification.

The Short-Form Health Surveys are a group of scales providing a general measure of self-rated health. Whilst the SF-36 has been extensively tested and used within Australia, a briefer form, the SF-12 version 1 (Ware, Kosinski, & Keller, 1995) was chosen for brevity. The SF-12 rates 8 domains of health, across the last 4 weeks; physical functioning, role functioning related to physical problems, bodily pain, general health, vitality, social functioning, role functioning related to emotional problems, and mental health. These domains then combine to form a physical component summary (PCS) score and mental component summary (MCS) score. For each scale, scores range between 0-100, with higher scores equating to better

health. Norms from a South Australian population study were chosen as the most up-to-date and representative Australian norms (Avery, Dal Grande, & Taylor, 2004). Those scoring more than 2 standard deviations below the mean were identified as the at risk group (physical component summary score ≤28.62 and mental component summary score ≤34.79).

The Kessler Psychological Distress Scale (K-10: Kessler & Mroczek, 1994) is a 10-item questionnaire providing a global indication of anxiety and depression symptoms. Symptoms experienced over the past four weeks are rated on a 5 point scale ranging from 'none of the time' to 'all of the time'. Whilst different cut-off scores are used within Australia, the convention set by the Australian Bureau of Statistics (2003) was followed, with total scores equal to or above 22, taken as an indication of high psychological distress. Andrews and Slade (2001) found that the K-10 appropriately identified those classified by the Composite International Diagnostic Interview v2.0, as having any DSM-IV or ICD-10 anxiety or affective diagnosis (at a score of 22; sensitivity=0.55, specificity=0.95).

Alcohol use was assessed using the AUDIT-C; a shortened version of the well-established Alcohol Use Disorders Identification Test (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). The AUDIT-C is scored on a scale of 0-12, with each question scored between 0 and 4. Different cut-off scores are recommended for men (Bush et al., 1998) and women (Bradley et al., 2003), with hazardous drinking identified through a score of 3 or more in women (sensitivity=0.66, specificity=0.94) and 4 or more in men (sensitivity=0.48, specificity=0.99).

The Severity of Dependence Scale (Gossop et al., 1995) was used to screen for benzodiazepine dependence. The SDS is a short 5-item scale that can be used to measure the degree of dependence on different types of drugs. Each SDS item is concerned with a psychological component of dependence. The diagnostic capability of the SDS was established in a sample of 100 regular benzodiazepine users (de Las Cuevas, Sanz, De Las Fuente, Padilla, & Berenguer, 2000). A score

above 6 corresponded with benzodiazepine dependence, as determined by the Composite International Diagnostic Interview (specificity=94.2%, sensitivity=97.9%).

The use of cannabis or other illicit drugs in the past 12 months was recorded, and non-users were compared to those who had any level of use. Likewise major categories of prescribed medications were enquired about (including antidepressants, antipsychotics, opioids, other psychotropic medications, other painkillers, and over-the-counter codeine use), with those who had taken these medications in the past 12 months, compared to those who had not. Medications examined in the 'other psychotropic category' included; acamprosate, buspirone, buproprion, clonidine, doxylamine, disulfiram, lithium, melatonin, naltrexone, varenicline, zolpicolone, and zolpidem.

To clarify benzodiazepine use, participants were questioned on the duration and frequency of their use. This information was then used to guide a post-hoc development of three different categories of benzodiazepine chronicity. In the survey participants were asked to indicate which answer best reflected their pattern of benzodiazepine use: use daily for – less than a month, greater than a month, or greater than a year; or use occasionally for – less than a month, greater than a month, or greater than a year. At the point of analysis this self-identified pattern was verified with information from other survey questions, including; start and finish date of using benzodiazepines, total days using benzodiazepines, and number of days in last month using benzodiazepines. In order to have sufficient numbers in each chronicity group, a pragmatic decision was made to combine some of these self-identified patterns of use into three groups with distinct patterns of chronicity. The three chronicity groups developed were as follows; short-term users (those who had been using *daily* or *occasionally* for *less than one year*), intermittent users (those who had used *occasionally*, for a period *greater than one year*) and chronic users (those who had used *daily* for a period *greater than one year*). The development of the chronicity groups was guided by the following considerations; (1) allocating sufficient participant numbers to each group, (2) promoting

homogeneity within each group and (3) allowing comparisons to be made across key elements of interest, namely the different effects of *duration* and *frequency* of use. An additional benzodiazepine variable was created focusing on monthly dosage. Reported doses for all benzodiazepine types were re-calculated to an equivalent diazepam dose (Drug and Alcohol Services South Australia, 2014); based on a defined daily dose of 10mg (World Health Organisation, 2011), a cut-off score of 300mg diazepam equivalent/month was used.

Table 2. *Rationale for Inclusion of Predictor Variables.*

Factor	Categorisation *(at risk, low risk)*[a]	Included because of previous association with:
Age	30 years plus, 0-30 years	*Accidents* (Bureau of Infrastructure, 2014; Simpson et al., 2005; Wadsworth, Simpson, et al., 2003) *Injuries* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003; Wadsworth, Simpson, et al., 2003) *Cognitive failures* (Simpson et al., 2005; Wadsworth, Simpson, et al., 2003),
Sex	Male, Female	*Accidents* (Bureau of Infrastructure, 2014; Simpson et al., 2005) *Injuries* (Pointer, 2013) *Cognitive failures* (Simpson et al., 2005),
Highest level of Education	< Grade 10, Grades 11-12[b] or TAFE/trade, University Degree	*Accidents* (Cubbin & Smith, 2002) *Injuries* (Cubbin & Smith, 2002) *Cognitive failures* (Wadsworth, Simpson, et al., 2003; Weinborn, Woods, O'Toole, Kellogg, & Moyle, 2011),
Income (weekly)[c]	≤$600/week, >$600/week	*Accidents* (Cubbin & Smith, 2002) *Injuries* (Cubbin & Smith, 2002; Simpson et al., 2005), *Cognitive failures* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003; Wadsworth, Simpson, et al., 2003),
Employment Status	Not employed, Part or Full-time employment	*Accidents* (Australian Bureau of Statistics, 2011) *Injuries* (Simpson et al., 2005; Wadsworth, Simpson, et al., 2003) *Cognitive failures* (Simpson et al., 2005; Wadsworth, Simpson, et al., 2003),
Relationship Status	Non-partnered, Partnered	*Accidents* (Wadsworth, Moss, et al., 2003) *Injuries* (Wadsworth, Moss, et al., 2003)

Factor	Categorisation *(at risk, low risk)*[a]	Included because of previous association with:
Physical health problems	SF8-PCS[d] cut-off ≤2SD population; ≤ 28.62, >28.63 *and* Chronic health condition reported[e], Nil chronic health condition	*Accidents* (Simpson et al., 2005) *Injuries* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003) *Cognitive failures* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003)
Mental health problems	SF8-MCS[f] cut-off ≤2SD population; ≤ 34.79, >34.80 *and* Kessler-10[g] score; 22-50,0-21	*Accidents* (Hilton & Whiteford, 2010; Simpson et al., 2005) *Injuries* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003; Wadsworth, Simpson, et al., 2003) *Cognitive failures* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003; Wadsworth, Simpson, et al., 2003)
Alcohol Consumption	Risky drinking /AUDIT[h] score; Women: 3-12,0-2 Men: 4-12, 0-3	*Accidents* (Bureau of Infrastructure, 2014; Movig et al., 2004; Simpson et al., 2005) *Injuries* (Burger, Lichtenstein, Hays, & Decker, 1990) *Cognitive failures* (Griffiths et al., 2012; Heffernan, Moss, & Ling, 2002)
Any cannabis use	Used in past 12 months, Nil use	*Accidents* (Kelly, Darke, & Ross, 2004; Wadsworth, Moss, Simpson, & Smith, 2006) *Injuries* (Barrio et al., 2012; Wadsworth et al., 2006) *Cognitive failures* (Bartholomew, Holroyd, & Heffernan, 2010; Matthews & Bruno, 2011; Montgomery, Seddon, Fisk, Murphy, & Jansari, 2012)
Other Illicit Drug Use (E.g. Speed or Ecstasy)	Used in past 12 months, Nil use	*Accidents* (Kelly et al., 2004; Raes et al., 2008) *Cognitive failures* (Iudicello et al., 2011; Rendell, Mazur, & Henry, 2009)
Antidepressant Use	Used in past 12 months, Nil use	*Accidents* (Chang et al., 2012; Wadsworth, Moss, et al., 2003; Wadsworth et al., 2005) *Injuries* (Wadsworth, Moss, et al., 2003; Wadsworth et al., 2005) *Cognitive failures* (Wadsworth, Moss, et al., 2003; Wadsworth et al., 2005) *Possible Sedation* (Australian Medicines Handbook, 2015)
Antipsychotic Use	Used in past 12 months, Nil use	*Cognitive failures* (Horia et al., 2006) *Possible Sedation* (Australian Medicines Handbook, 2015)
Opioid Use	Used in past 12 months, Nil use	*Accidents* (Hulse, English, Milne, & Holman, 1999; Kelly et al., 2004; Raes et al., 2008) *Injuries* (Majdzadeh et al., 2009) *Cognitive failures* (Terrett et al., 2014) *Sedation* (Australian Medicines Handbook, 2015)
Other Psychotropic Use[i]	Used in past 12 months, Nil use	*Accidents* (Chang et al., 2012; Gustavsen et al., 2008) *Sedation* (Australian Medicines Handbook, 2015)
Over-the-counter Codeine Use	Used in past 12 months, Nil use	*Sedation* (Australian Medicines Handbook, 2015)

Factor	Categorisation *(at risk, low risk)*[a]	Included because of previous association with:
Other Painkillers	Used in past 12 months, Nil use	*Sedation* (Australian Medicines Handbook, 2015)
Benzodiazepine Use	Chronicity of use; Chronic use, Intermittent use, Short-term use *and* Monthly Dose; Equivalent diazepam dose; >301mg, 0-300mg	*Accidents* (Chang et al., 2012; Kelly et al., 2004; Movig et al., 2004) *Injuries* (Wadsworth et al., 2005) *Cognitive failures* (Barker, Greenwood, Jackson, & Crowe, 2004b; Rich et al., 2006; Wadsworth et al., 2005)

[a]Predictor variables were used a categorical variables, and were separated into 'at risk' and 'low risk' groups, based on findings and cut-off scores from previous literature. In the regression analyses, the 'low risk' categories were the baseline group, and the 'at risk' categories were the comparison group. [b]In Australia, Grade 11 students are normally 16-17 years of age, and are typically in their twelfth year of education. [c]This weekly cut-off was chosen as it was the income range provided in the questionnaire most representative of the June 2014 poverty line for a single working adult of $509.53; if the income for a family unit is less than the applicable poverty line, they are considered to be in poverty (Melbourne Institute of Applied Economic and Social Research, 2014). This amount does not take into account the presence of other dependent family members. [d]Short-Form Health Survey-8 – Physical Component Score (Ware, Kosinski, & Keller, 1995). [e]The following chronic conditions were specified: chronic pain, sleep apnoea, neurological conditions, chronic lung disease, depression, anxiety, substance dependence, another mental health condition, any other chronic condition. [f]Short-Form Health Survey-8 – Mental Component Score (Ware, Kosinski, & Keller, 1995) [g]Kessler Psychological Distress Scale (K-10: Kessler & Mroczek, 1994). [h]Alcohol Use Disorders Identification Test (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993. [i]Other psychotropic medications included: acamprosate, buspirone, buproprion, clonidine, doxylamine, disulfiram, lithium, melatonin, naltrexone, varenicline, zolpicolone, and zolpidem.

Analysis

Using SPSS (Version 22) univariate logistic regression was conducted to examine associations between various demographic, health factor, and drug use predictor variables, and the dependent measures; driving accidents (ever, 12 months), driving close calls, general accidents, minor injuries (12 months, one month), prospective memory problems, and retrospective memory problems. The predictor variables were categorical, divided into 'at risk' or 'low risk' classifications. For each variable the 'low risk' group was used as the baseline group in the analysis, and the 'at risk' group was used as the comparison group. Therefore, an odds ratio of >1, means that the outcome variable is more likely to occur in the comparison group compared to the baseline group. The exceptions to this classification system were the 'education' and 'benzodiazepine chronicity' variables which were used as

categorical three-level predictors, in order to capture the variation within the variable. The benzodiazepine chronicity variable was coded so that the baseline group was the category of key interest – the chronic users. This means that for this variable an odds ratio of <1 means that the safety incident was *more* likely to occur in the chronic user group. Due to the large number of predictor variables, the chance of Type I errors was high. Given that the current sample size was small, the decision was made to also run a bootstrapping analysis. Bootstrapping is a general resampling procedure and was used to aid in interpretation of results.

To understand the unique effects of benzodiazepine use, a multivariate logistic regression analysis was run, using a hierarchical stepwise model. Due to high multicollinearity the following variables were excluded from the multivariate analysis; education, income, SF-12 mental component score, other painkiller use, and any chronic condition. Model 1 included the benzodiazepine chronicity variable only. Model 2 added demographic factors (age, sex, employment, partnered). Model 3 added health factor variables (SF-12 physical component score, Kessler-10) and Model 4 added the remaining drug use variables (AUDIT-C, cannabis use, other illicit drug use, antidepressant use, antipsychotic use, opioid use, other psychotropic use, over-the-counter codeine use and monthly benzodiazepine dose). This series of stepwise models allowed the exploration of both the unique effects of benzodiazepine on the outcome variables, and the effects in context of other key correlated variables. Due to a relatively low sample size, power in this study was affected. In order to aid identification of effects, results with a significance of <0.1, are reported on.

RESULTS

Sample Characteristics

The mean age of participants (*n*=129) was 38.15 years (*SD*=13.47), with an age range from 18-72 years. Slightly over half of the participants were female (*n*=71; 55%). The sample was quite highly educated with almost half having completed or

were completing a University degree (*n*=64, 55.2%), whilst almost a third (*n*=32, 27.6%) had completed year 11 or 12, or a TAFE /trade course. Only 17.2% of the sample had completed less than year 10. The sample was evenly split between those in work (part or full-time) compared to those who were unemployed (*n*=64, 50.0%). The most common income bracket reported by 19.3% of participants was $250-399/week ($13,000-20,799/year). While reported income ranged between a 'negative income' up to a highest income bracket of $2000 or more/week, slightly over half the sample (*n*=61, 51.3%) fell below the poverty line (<$600/week).

The average K-10 score within the sample was 24.48 (*SD*=9.59). Half scored above the K-10 cut-off score, suggesting high levels of psychological distress (*n*=51, 52%). Similarly, the average SF-12 mental component score was 37.27 (*SD*=13.43), with half scoring more than two standard deviations below the population mean (*n*=51, 50%). Physical health, as measured by the SF-12 physical component score, was close to the general population mean, with an average score of 45.81 (*SD*=12.39); only a small percentage of participants scored more than two standard deviations below the population mean on the PCS (*n*=11, 10.8%).

Use of medication in the sample was high. In addition to benzodiazepines, over a third of the group had used at least one antidepressant in the past 12 months (35.7%), with the most common preparations being sertraline and escitalopram. Antipsychotics were used by 14% of the sample; most commonly used were quetiapine (10.9%) and olanzapine (3.1%). Almost a quarter of the participants reported using opioids (24%), most commonly prescription-only codeine (16.3%). Similar proportions had used other types of psychotropic medications (22.5%), with the active ingredients most commonly used being doxylamine (7%) and zolpidem (8.5%).

Most of the sample reported using benzodiazepines for sleep only (*n*=59, 45.7%) or anxiety only (*n*=54, 41.9%), with only a small group reporting use for other or multiple reasons (*n*=16, 12.4%). Using the Severity of Dependence Scale (Gossop et al., 1995) to screen for benzodiazepine dependence revealed that most of the

participants (*n*=80, 68.4%) scored between 0-6 (i.e. below problem level), with 31.6% (*n*=37) of the sample scoring above 7, thus indicating possible benzodiazepine dependence (de Las Cuevas et al., 2000).

The benzodiazepine chronicity categories were developed according to participant's self-reported pattern of use; short-term, intermittent, and chronic. Table 3 explores the variation between each category of chronicity on key variables. Short-term users, self-identified as having used benzodiazepines for less than one year were, as expected, the group with the shortest duration of use in the sample. Despite this, on average, their duration of use was far beyond the recommended four-week period. On average they used benzodiazepines half the days in a month, and their total monthly dose was comparable to 10mg of diazepam per day. Intermittent users showed a similar pattern to the short-term users, regarding days used per month and total dose per month, but as expected their average duration of use was significantly longer, at 6.5 years. Chronic benzodiazepine users, however, were a vastly different group; their average use was over 8 years. Although, this number may have been inflated by the use of multiple benzodiazepines, and there may have been periods of non-use during this time. In the chronic users, the average 'total days used per month' was greater than 30; as this figure was additive across different preparations, this indicates the use of multiple benzodiazepines simultaneously. The average total dose per month used by the chronic group was over 900mg (diazepam equivalent). Whilst a monthly dose of this size could feasibly be achieved by a standard 10mg three times a day for anxiety, current clinical guidelines would not support this high level of use for the long periods identified by this group. Univariate results are presented in Tables 4, 5, and 6, and Multivariate results in Tables 7, 8, and 9.

Table 3. *Analysis of Variance for Key variables of interest across each Benzodiazepine Chronicity Category*

	Short-term Use *(SD)*[a] *N=24*	Intermittent Use *(SD)* *N=55*	Chronic Use *(SD)* *N=50*	ANOVA	Significant comparisons[b]
Reason for Benzodiazepine Use					
Sleep only	*n*=9 (37.5%)	*n*=27 (49.1%)	*n*=23 *(46.0%)*	n/a	
Anxiety only	*n*=12 (50%)	*n*=20 (36.4%)	*n*=22 (44%)	n/a	
Other/multiple reasons	*n*=3 (12.5%)	*n*=8 (14.5%)	*n*=5 (10%)	n/a	
Benzodiazepine Use					
Mean Length of Use - days[c]	168.8 *(243.8)*	2416.7 *(3840.8)*	3053.9 *(3605.1)*	*F*(2,126)=6.05, *p*=.003	ST<Int, *p*=.020; ST<Chr *p*=.002
Mean Total days used per month	14.9 *(17.7)*	10.3 *(13.9)*	38.1[d] *(45.6)*	*F*(2,115)=10.65, *p*<.001	ST<Chr, *p*=.013; Int<Chr, *p*<.001
Mean Total Dose per month[e]	229.5[f] *(381.9)*	231.6 *(432.1)*	919.3 *(1816.4)*	*F*(2,115)=4.81, *p*=.010	Int<Chr, *p*=.013
Other variables of interest					
Mean Age	30.9 *(11.9)*	39.1 *(14.7)*	40.5 *(11.7)*	*F*(2,126)=4.64, *p*=.011	ST<Int, *p*=.031; ST<Chr, *p*=.010
Mean AUDIT-C[g]; Average Score	4.1 *(3.6)*	4.2 *(3.2)*	3.5 *(3.5)*	*F*(2,102)=0.54, *p*=.587	-
Mean Kessler-10[h]	27.1 *(8.3)*	21.5 *(8.3)*	27.8 *(10.5)*	*F*(2,95)=5.35, *p*=.006	Int<Chr, *p*=.008
Mean SF-12 MCS[i]	33.0 *(11.9)*	40.5 *(13.1)*	35.6 *(14.0)*	*F*(2,99)=2.60, *p*=.079	-
Mean SF-12 PCS[j]	47.4 *(11.3)*	47.6 *(12.3)*	43.1 *(12.8)*	*F*(2,99)=1.54, *p*=.219	-
Mean GP visits (past year)	9.1 *(8.8)*[k]	6.7 *(5.2)*	12.4 *(8.4)*	*F*(2,107)=7.002, *p*=.001	Int<Chr, *p*=.001
Mean Average score BZD SDS[l]	4.2 *(4.1)*	2.6 *(3.3)*	7.3 *(4.4)*	*F*(2,114)=18.87, *p*<.001	ST<Chr, *p*=.008; Int<Chr, *p*=<.001

Benzodiazepine chronicity categories: Short-term Use (using benzodiazepines daily or occasionally for less than one year), Intermittent Use (using benzodiazepines occasionally for greater than one year), Chronic Use (using benzodiazepines daily for greater than one year).
[a]*SD=Standard Deviation.* [b]Tukey's method used for post-hoc tests. ST=short-term group. Int=intermittent group. Chr=Chronic group. [c]Calculated using start and finish dates for each benzodiazepine, therefore does not represent the number of days on which benzodiazepines have been consumed, but rather the period of time that benzodiazepines have been used for. Additionally, this total is additive across each benzodiazepine type used. [d]This is a cumulative sum across all benzodiazepine types, therefore the mean of 38.13 for chronic users reflects the use of more than one benzodiazepine a day. [e]Converted to an equivalent diazepam dose in milligrams. [f]This monthly amount is equivalent to 7.63mg a day, which is less than the 10mg defined daily dose. [g]Kessler-10 (Kessler & Mroczek, 1994); total scores ≥22, were taken as an indication of high psychological distress. [h]Different cut-off scores are recommended for men (Bush et al., 1998) and women (Bradley et al., 2003), on the AUDIT-C with hazardous drinking identified through a score of 3 or more in women (sensitivity=0.66, specificity=0.94) and 4 or more in men (sensitivity=0.48, specificity=0.99). [i]Mental Component Score; scores range between 0-100, with higher scores equating to better health. [j]Physical Component Score: scores range between 0-100, with higher scores equating to better health [k]In this group there was a participant who identified as having 300 GP visits in the past year. This extreme outlier was removed as it severely inflated the result for this short-term user group, and was most likely an error during survey completion. [l]BZD=benzodiazepine, SDS=Severity of Dependence Scale. A score above 6 corresponds with benzodiazepine dependence, as determined by the Composite International Diagnostic Interview (specificity=94.2%, sensitivity=97.9%).

Traffic Incidents

In the sample, 93.7% had driven a car, with 90.7% (*n*=107) having a full license (car, motorbike, taxi or heavy), and 7.6% of the sample having only a learners, provisional or restricted licence. A large proportion of the group (*n*=75, 65.2%) had held their longest licence for over 10 years. Half the sample (*n*=58, 50.9%) reported they usually drove every day of the week, with the average estimated distance driven each week being 206.27kms (*SD*=288.58; range 3-2000kms). Most of the sample reported that they had never lost their licence due to a traffic offence (*n*=90, 81.8%), nor had lost any demerit points in the last 12 months (*n*=83, 74.8%).

Road Traffic Accident – Ever

Half of the sample reported experiencing at least one road traffic accident, whilst the driver, in their lifetime (50.87%; 95%CI 41.82-59.87). The intermittent benzodiazepine use group were twice as likely to report ever experiencing an accident, compared to daily chronic users. People with a chronic health condition were almost three times more likely to have ever experienced an accident. Those who were below the poverty line, and/or unemployed were less likely to report ever experiencing a road traffic accident, which may be a reflection of time spent on the road and peak hour driving. People who had completed year 11 & 12 or a TAFE/trade course, were half as likely to ever experience a traffic accident compared to those who had gone to university. In the multivariate analysis examining lifetime experience of traffic accidents, only 34.8% of the variance was explained by the final model. This was not unexpected given that most of the predictor variables were focused on events occurring in the last 12 months or less, in comparison to the outcome variable which assessed lifetime traffic accident occurrences. Despite this, the significance of benzodiazepine use increased as more factors were added in, and in the final model, the intermittent user group were more than four times more likely than the chronic user group to report ever experiencing a traffic accident. In model 4 there was a negative association with being unemployed, use of other psychotropics, and ever experiencing a traffic

accident. Those who had used antipsychotics were five times more likely to have ever experienced a traffic accident.

Road Traffic Accident – 12 months

In this sample 14.91% reported experiencing a traffic accident whilst the driver, in the last 12 months (95%CI 9.52-22.59). Univariate analysis revealed a significant effect of benzodiazepine dosage. People using greater than 300mg diazepam equivalent/month of benzodiazepines were up to three times more likely to report a traffic accident in the last 12 months. Those reporting a traffic accident in the last 12 months were also significantly more likely to be under 30 years of age, to report other illicit drug use, to use other painkillers, or be unpartnered. In the multivariate analysis, 61.8% of the variance was explained by model 4, and the only significant predictor was the use of other psychotropics, which was negatively associated with the risk of an accident in the past 12 months.

Traffic Near Misses.

Near miss traffic incidents were reported by 38.60% of the sample (95%CI 30.17-47.77). Univariate analysis showed associations between those who were under 30 years of age, unpartnered, those reporting mental health problems, high psychological distress, cannabis use and illicit drug use, and an increased incidence of traffic near misses. The final multivariate model explained 61.2% of the total variance. Significant predictors in this final model included being female, under 30 years, unemployed, or unpartnered.

Non-traffic General Incidents:

General Accidents.

General accidents were experienced by 22.94% of the sample (95%CI 16.05-31.67). Percentages described in the next section, refer to the percentage of the sample reporting each experience. The most common type of non-traffic accident, reported

by 7.8% of the sample, was a 'slip, trip or fall on the same level', with the area of the body most commonly reported to be injured being the hands (9.3%), followed by the head (7%). The types of damage most commonly reported was bruising (10.9%), followed by lacerations (open cuts and wounds; 10.1%). Most accidents were then treated at the Emergency department (11.6%) or by the GP (10.1%). Chronic daily benzodiazepine use, was associated with significantly higher rates of general accidents, compared to those the intermittent user group. Other variables significantly associated with increased risk of general accidents included being under 30 years of age, being unpartnered, having mental health problems, or high psychological distress, illicit drug use, and use of over-the-counter codeine, or prescribed painkillers. Notably the use of antipsychotics was associated with a seven fold greater risk of accidents. The final multivariate model explained 68.7% of the variance in the sample. Chronic use of benzodiazepines remained a significant predictor throughout each model. In the final model, being under 30 years, being unpartnered, using antipsychotics, or over-the-counter codeine, were significant predictors of increased general accidents. The use of other psychotropic medication was inversely associated with general accidents.

Frequent Minor Injuries – 12 months

In this sample, 16.07% had experienced frequent minor injuries over the last 12 months (95%CI 10.41-23.98). There were few significant predictors in the univariate analysis; significant associations were found between being younger, unpartnered, having mental health problems, the use of other psychotropics, and having frequent minor injuries. The only significant predictor in the multivariate analysis, was being under 30 years of age, with 50.2% of the variance explained by the final model.

Frequent Minor Injuries – One month

Only 8.18% (95%CI 4.36-14.82) of the sample experienced frequent minor injuries in the last month. Univariate analysis revealed those who were under 30 years of age, or used other psychotropic medications were at a significant risk of minor injuries

over the past month. There was a notable 7 times greater risk of recent minor injuries for those reporting psychological distress. The multivariate analysis was not able to be run due to the small number of participants reporting problems over the last month.

Cognitive Failures

Cognitive failures were assessed using the Prospective Retrospective Memory Questionnaire (Smith, Della Sala, Logie, & Maylor, 2000), which allows two scores to be calculated measuring prospective memory and retrospective memory.

Prospective Memory Problems

In this group 19.61% experienced prospective memory problems; defined as scoring ≥1SD above the population mean (95%CI 13.07-28.35). Chronic daily benzodiazepine use, was associated with a significantly increased risk of prospective memory problems compared to those who used long-term but only intermittently. Taking more than 300mg diazepam equivalent of benzodiazepines per month was also associated with prospective memory problems. Reporting poor mental health was significantly associated with almost a 14 times greater risk, and psychological distress, with a 6 times greater risk, of prospective memory problems. Other significant predictors in the univariate model included being under 30 years, being female, and using antidepressants, or antipsychotics. Surprisingly, there was an inverse association between using over-the-counter codeine and prospective memory problems. In the multivariate analysis, the final model explained 59.3% of the variance. Chronic benzodiazepine use remained a significant predictor in all but the final model. Being over 31 years old, and the use of over-the-counter codeine remained negatively associated with prospective memory problems in the final model.

Retrospective Memory Problems.

Retrospective memory problems (scores ≥1SD above the population mean) were reported by 22.47% of this sample (95%CI 15.04-22.47). Chronic benzodiazepine use was associated with a significantly increased risk of retrospective memory problems compared to intermittent use. Other associated predictors in the univariate analysis included being female, unemployed, having mental health problems, high psychological distress, or using antipsychotics. In the multivariate analysis, 75% of the variance was explained by the final model, and chronic benzodiazepine use remained associated with a higher risk of retrospective memory problems. Being female, unemployed, and using opioids were associated predictors in the final model.

Table 4. *Univariate Logistic Regression Predicting Likelihood of Traffic Incidents*

	Road Traffic Accident – Ever (Have ever had an accident, whilst the driver) *n*=114					**Road Traffic Accident – last 12 months** (Have had accident in last 12 months, whilst the driver) *n*=114					**Traffic Near misses – last 12 months** (A traffic incident almost resulting in a crash, whilst the driver) *n*=114				
Predictor Variables Comparison Groups	**No Accident % (n=56)**	**Accident % (n=58)**	**OR (significance)**	**Bootstrapped significance**	**95%CI**	**No Accident % (n=97)**	**Accident % (n=17)**	**OR (significance)**	**Bootstrapped significance**	**95%CI**	**No Near Miss % (n=70)**	**Near Miss % (n=44)**	**OR (significance)**	**Bootstrapped significance**	**95%CI**
Demographic characteristics															
Age: ≥31 years	*66.1*	*58.6*	*0.73 (0.412)*	*0.435*	*0.34-1.56*	*67.0*	*35.3*	***0.27 (0.017)***	***0.010***	*0.09-0.79*	*81.4*	*31.8*	***0.11 (<0.001)***	***0.001***	*0.04-0.26*
Male	*39.3*	*44.8*	*1.26 (0.549)*	*0.562*	*0.60-2.65*	*43.3*	*35.3*	*0.71 (0.539)*	*0.512*	*0.24-2.09*	*47.1*	*34.1*	*0.58 (0.171)*	*0.171*	*0.27-1.27*
Education:			*(0.249)*					*(0.710)*					*(0.610)*		
- University (baseline group)	*50.0*	*64.7*				*56.7*	*61.5*				*54.5*	*62.2*			
- Year 11/12 or Tafe/trade	*30.8*	*17.6*	***0.44 (0.098)***	*0.522*	*0.17-1.16*	*25.6*	*15.4*	*0.55 (0.477)*	*0.754*	*0.11-2.82*	*24.2*	*24.3*	*0.88 (0.797)*	*0.309*	*0.33-2.32*
- < Year 10	*19.2*	*17.6*	*0.71 (0.516)*	*0.440*	*0.25-2.00*	*17.8*	*23.1*	*1.20 (0.808)*	*0.288*	*0.28-5.05*	*21.2*	*13.5*	*0.56 (0.320)*	*0.500*	*0.18-1.76*
Income (<$13,000)	*58.0*	*40.0*	***0.48 (0.067)***	***0.067***	*0.22-1.05*	*50.0*	*40.0*	*0.67 (0.475)*	*0.463*	*0.22-2.03*	*45.5*	*53.8*	*1.40 (0.406)*	*0.449*	*0.63-3.10*
Unemployed	*61.8*	*36.2*	***0.35 (0.007)***	***0.007***	*0.16-0.75*	*51.0*	*35.3*	*0.52 (0.236)*	*0.229*	*0.18-1.53*	*47.1*	*51.2*	*1.18 (0.678)*	*0.699*	*0.55-2.51*
Unpartnered	*51.9*	*62.5*	*1.54 (0.268)*	*0.271*	*0.72-3.32*	*53.8*	*76.5*	***2.79 (0.093)***	***0.062***	*0.84-9.19*	*44.8*	*78.0*	***4.39 (0.001)***	***0.001***	*1.81-10.60*
Health factors															
Physical health Problems: PCS[a]	*8.9*	*11.8*	*1.37 (0.646)*	*0.629*	*0.36-5.19*	*12.0*	*0.0*	*0.00 (0.999)*	*0.001*	*-*	*31.1*	*5.7*	*0.40 (0.266)*	*0.127*	*0.08-2.01*
Mental health Problems: MCS[b]	*40.0*	*54.9*	*1.83 (0.146)*	*0.152*	*0.81-4.12*	*45.8*	*61.5*	*1.90 (0.296)*	*0.283*	*0.57-6.28*	*41.0*	*60.0*	***2.16 (0.075)***	***0.067***	*0.93-5.04*
Psychological Distress: K-10[c]	*47.8*	*52.1*	*1.19 (0.680)*	*0.690*	*0.53-2.66*	*47.6*	*66.7*	*2.21 (0.225)*	*0.192*	*0.62-7.90*	*41.7*	*64.7*	***2.57 (0.034)***	***0.030***	*1.08-6.13*
Chronic Health Conditions	*67.9*	*86.2*	***2.96 (0.023)***	***0.020***	*1.16-7.53*	*78.4*	*70.6*	*0.66 (0.484)*	*0.495*	*0.21-2.09*	*80.0*	*72.7*	*0.67 (0.369)*	*0.376*	*0.28-1.62*
Drug use															
Risky drinking: AUDIT-C[d]	*57.4*	*54.7*	*0.90 (0.784)*	*0.808*	*0.41-1.98*	*54.7*	*64.3*	*1.49 (0.503)*	*0.499*	*0.46-4.83*	*50.8*	*64.9*	*1.79 (0.173)*	*0.181*	*0.78-4.13*
Cannabis use	*34.0*	*28.6*	*0.78 (0.564)*	*0.559*	*0.33-1.84*	*29.8*	*41.7*	*1.69 (0.409)*	*0.384*	*0.49-5.82*	*23.3*	*44.4*	***2.63 (0.033)***	***0.041***	*1.08-6.35*
Other Illicit Drug Use	*21.3*	*26.0*	*1.30 (0.585)*	*0.589*	*0.51-3.34*	*20.2*	*46.2*	***3.38 (0.049)***	***0.034***	*1.00-11.37*	*16.7*	*35.1*	***2.71 (0.041)***	***0.033***	*1.04-7.06*
Antidepressant Use	*37.5*	*39.7*	*1.10 (0.813)*	*0.808*	*0.52-2.33*	*36.1*	*52.9*	*1.99 (0.193)*	*0.188*	*0.71-5.63*	*35.7*	*43.2*	*1.37 (0.426)*	*0.434*	*0.63-1.37*
Antipsychotic Use	*10.7*	*19.0*	*1.95 (0.222)*	*0.209*	*0.67-6.69*	*14.4*	*17.6*	*1.27 (0.732)*	*0.694*	*0.32-5.00*	*12.9*	*18.2*	*1.51 (0.439)*	*0.431*	*0.53-4.25*
Opioid Use	*19.6*	*31.0*	*1.84 (0.166)*	*0.163*	*0.78-4.36*	*22.7*	*41.2*	*2.39 (0.113)*	*0.110*	*0.81-7.00*	*27.1*	*22.7*	*0.79 (0.599)*	*0.602*	*0.33-1.90*
Other Psychotropic Use	*25.0*	*20.7*	*0.78 (0.584)*	*0.592*	*0.33-1.88*	*22.7*	*23.5*	*1.05 (0.939)*	*0.933*	*0.31-3.54*	*21.4*	*25.0*	*1.22 (0.658)*	*0.658*	*0.50-2.98*
OTC[e] Codeine Use	*53.2*	*60.0*	*1.32 (0.499)*	*0.496*	*0.59-2.95*	*55.3*	*66.7*	*1.62 (0.460)*	*0.441*	*0.45-5.78*	*52.5*	*63.9*	*1.60 (0.274)*	*0.275*	*0.69-3.74*
Prescribed painkillers	*27.7*	*38.0*	*1.60 (0.281)*	*0.287*	*0.68-3.78*	*29.4*	*58.3*	***3.36 (0.055)***	***0.030***	*0.97-11.60*	*31.1*	*36.1*	*1.25 (0.616)*	*0.640*	*0.52-2.98*
Monthly BZD Dose: >300mg[g]	*34.0*	*33.3*	*0.97 (0.943)*	*0.943*	*0.43-2.19*	*29.5*	*56.3*	***3.07 (0.044)***	***0.032***	*1.03-9.11*	*32.8*	*35.0*	*1.10 (0.818)*	*0.820*	*0.48-2.54*
Benzodiazepine Chronicity:[f]			*(0.107)*					*(0.406)*					*(0.293)*		
- Chronic Use (baseline group)	*41.1*	*31.0*				*35.1*	*41.2*				*40.0*	*29.5*			
- Intermittent Use	*35.7*	*55.2*	***2.04 (0.092)***	***0.078***	*0.89-4.70*	*44.3*	*52.9*	*1.02 (0.976)*	*0.970*	*0.34-3.01*	*45.7*	*45.5*	*1.35 (0.500)*	*0.502*	*0.59-3.19*
- Short-term	*23.2*	*13.8*	*0.79 (0.661)*	*0.661*	*0.27-2.30*	*20.6*	*5.9*	*0.24 (0.200)*	*0.104*	*0.03-2.12*	*14.3*	*25.0*	*2.37 (0.117)*	*0.117*	*0.81-6.98*

*Table Interpretation: The variables listed are the comparison group. This means that the percentages reported are the percentages in the comparison group that either did or did not experience an event. Regarding the odds ratio (OR), an OR>1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. For example, as reported above, of those who *had not* experienced a traffic accident in the last 12 months, 20.2% had used 'other illicit drugs', for those who *had* experienced an accident, 46.2% had used 'other illicit drugs'. Those who had used 'other illicit drugs' were 3.38 times more like to experience an accident than those who had not. [a]SF-12 Physical Component Score, [b]SF-12 Mental Component Score, [c]Kessler-10, [d]Alcohol Use Disorders Identification Test-C, [e]Over-the-counter, [f]In the benzodiazepine chronicity category, the chronic benzodiazepine group was used as the reference category and the intermittent and short-term groups were compared to this. [g]A monthly benzodiazepine (BZD) dose cut-off score of 300mg (diazepam equivalent) was used. This is equivalent to the defined daily dose of 10mg/day (World Health Organisation, 2011) being used daily for a month.

Table 5. *Univariate Logistic Regression Predicting Likelihood of General Incidents*

	General Accident - 12 months (Accident requiring medical attention in last 12 months) *n*=109					**Minor Injuries – 12 months** (At least one minor injury in last 12 months) n=112					**Minor Injuries – 1 month** (At least one minor injury in last 1 month) *n*=110				
Predictor Variables **Comparison Groups**	**No Accident % (*n*=84)**	**Accident % (*n*=25)**	**OR (significance)**	**Bootstrapped significance**	**95%CI**	**No Minor Injury % (*n*=94)**	**Minor Injury % (*n*=18)**	**OR (significance)**	**Bootstrapped significance**	**95%CI**	**No Minor Injury % (*n*=101)**	**Minor Injury % (*n*=9)**	**OR (significance)**	**Bootstrapped significance**	**95%CI**
Demographic characteristics															
Age: ≥31 years	*69.0*	*44.0*	***0.35 (0.025)***	***0.022***	*0.14-0.88*	*69.1*	*38.9*	***0.28 (0.018)***	***0.010***	*0.10-0.81*	*67.3*	*22.2*	***0.14 (0.017)***	***0.005***	*0.03-0.70*
Male	*40.5*	*56.0*	*1.87 (0.173)*	*0.171*	*0.76-4.61*	*43.6*	*44.4*	*1.03 (0.948)*	*0.949*	*0.38-2.851*	*41.6*	*55.6*	*1.76 (0.422)*	*0.407*	*0.45-6.93*
Education:			*(0.661)*					*(0.423)*					*(0.869)*		
- University (baseline group)	*52.6*	*61.9*				*55.7*	*50.0*				*54.7*	*60.0*			
- Year 11/12 or Tafe/trade	*30.8*	*28.6*	*0.79 (0.669)*	*0.268*	*0.27-2.35*	*27.3*	*42.9*	*1.75 (0.359)*	*0.213*	*0.53-5.78*	*30.5*	*20.0*	*0.60 (0.662)*	*0.506*	*0.06-6.01*
- < Year 10	*16.7*	*9.5*	*0.49 (0.380)*	*0.475*	*0.10-2.44*	*17.0*	*7.1*	*0.47 (0.492)*	*0.118*	*0.05-4.10*	*14.7*	*20.0*	*1.24 (0.858)*	*0.158*	*0.12-12.84*
Income (<$13,000)	*44.9*	*60.9*	*1.91 (0.181)*	*0.206*	*0.74-4.94*	*47.7*	*44.4*	*0.88 (0.803)*	*0.827*	*0.32-2.44*	*47.3*	*55.6*	*1.39 (0.638)*	*0.666*	*0.35-5.51*
Unemployed	*47.0*	*48.0*	*1.04 (0.929)*	*0.927*	*0.43-2.55*	*49.5*	*33.3*	*0.51 (0.215)*	*0.216*	*0.18-1.48*	*46.0*	*55.6*	*1.47 (0.584)*	*0.563*	*0.37-5.79*
Unpartnered	*54.4*	*76.0*	***2.65 (0.061)***	***0.036***	*0.96-7.35*	*55.6*	*76.5*	***2.60 (0.117)***	***0.079***	*0.79-8.59*	*57.3*	*77.8*	*2.61 (0.247)*	*0.137*	*0.52-13.22*
Health factors															
Physical health Problems: PCS[a]	*12.7*	*4.8*	*0.35 (0.324)*	*0.157*	*0.04-2.86*	*11.8*	*5.9*	*0.47 (0.485)*	*0.231*	*0.06-3.93*	*11.8*	*0.0*	-	-	-
Mental health Problems: MCS[b]	*44.3*	*66.7*	***2.51 (0.074)***	***0.070***	*0.91-6.90*	*44.7*	*76.5*	***4.02 (0.023)***	***0.018***	*1.21-13.34*	*46.2*	*100.0*	-	-	-
Psychological Distress: K-10[c]	*44.9*	*77.8*	***4.30 (0.017)***	***0.009***	*1.30-14.24*	*48.8*	*68.8*	*2.31 (0.151)*	*0.135*	*0.74-7.24*	*49.4*	*87.5*	***7.16 (0.071)***	***0.048***	*0.85-60.61*
Chronic Health Conditions	*88.1*	*76.0*	*0.43 (0.141)*	*0.131*	*0.14-1.33*	*86.2*	*72.2*	*0.42 (0.149)*	*0.141*	*0.13-1.37*	*85.1*	*77.8*	*0.61 (0.561)*	*0.428*	*0.12-3.23*
Drug use															
Risky drinking: AUDIT-C[d]	*54.3*	*68.2*	*1.80 (0.247)*	*0.230*	*0.66-4.89*	*56.3*	*55.6*	*0.97 (0.952)*	*0.943*	*0.35-2.69*	*55.8*	*55.6*	*0.99 (0.989)*	*0.961*	*0.25-3.92*
Cannabis use	*28.2*	*45.5*	*2.12 (0.130)*	*0.128*	*0.80-5.62*	*30.6*	*35.3*	*1.24 (0.703)*	*0.716*	*0.41-3.71*	*31.2*	*25.0*	*0.74 (0.717)*	*0.592*	*0.14-3.87*
Other Illicit Drug Use	*20.3*	*40.9*	***2.73 (0.052)***	***0.039***	*0.99-7.50*	*22.1*	*35.3*	*1.93 (0.251)*	*0.236*	*0.63-5.88*	*23.4*	*25.0*	*1.09 (0.919)*	*0.780*	*0.21-5.80*
Antidepressant Use	*40.5*	*44.0*	*1.16 (0.754)*	*0.778*	*0.47-2.85*	*41.5*	*38.9*	*0.90 (0.837)*	*0.828*	*0.32-2.52*	*41.6*	*44.4*	*1.12 (0.868)*	*0.842*	*0.29-4.44*
Antipsychotic Use	*8.3*	*40.0*	***7.33 (<0.001)***	***0.001***	*2.41-22.32*	*13.8*	*27.8*	*2.40 (0.149)*	*0.125*	*0.73-7.85*	*14.9*	*33.3*	*2.87 (0.166)*	*0.110*	*0.65-12.73*
Opioid Use	*26.2*	*36.0*	*1.59 (0.342)*	*0.344*	*0.61-4.10*	*26.6*	*33.3*	*1.38 (0.559)*	*0.609*	*0.47-4.07*	*27.7*	*33.3*	*1.30 (0.721)*	*0.692*	*0.31-5.57*
Other Psychotropic Use	*23.8*	*32.0*	*1.51 (0.412)*	*0.425*	*0.57-4.01*	*23.3*	*44.4*	***2.78 (0.056)***	***0.038***	*0.97-7.94*	*23.8*	*55.6*	***4.01 (0.051)***	***0.030***	*1.00-16.14*
OTC[e] Codeine Use	*51.9*	*72.7*	***2.47 (0.087)***	***0.085***	*0.88-6.97*	*55.8*	*52.9*	*0.89 (0.828)*	*0.831*	*0.31-2.53*	*57.4*	*37.5*	*0.44 (0.286)*	*0.208*	*0.10-1.97*
Prescribed painkillers	*29.1*	*54.5*	***2.92 (0.030)***	***0.030***	*1.11-7.70*	*32.6*	*41.2*	*1.45 (0.495)*	*0.508*	*0.50-4.21*	*35.1*	*25.0*	*0.62 (0.566)*	*0.437*	*0.12-3.23*
Monthly BZD Dose: >300mg[g]	*32.1*	*45.8*	*1.79 (0.220)*	*0.217*	*0.71-4.56*	*35.6*	*29.4*	*0.75 (0.623)*	*0.608*	*0.24-2.33*	*34.0*	*37.5*	*1.16 (0.843)*	*0.794*	*0.26-5.18*
Benzodiazepine Chronicity:[f]			***(0.083)***					*(0.887)*					*(0.915)*		
- Chronic Use (baseline group)	*34.5*	*52.0*				*38.3*	*44.4*				*39.6*	*33.3*			
- Intermittent Use	*50.0*	*24.0*	***0.32 (0.037)***	***0.025***	*0.11-0.94*	*43.6*	*38.9*	*0.77 (0.641)*	*0.632*	*0.25-2.33*	*42.6*	*44.4*	*1.24 (0.786)*	*0.729*	*0.26-5.89*
- Short-term	*15.5*	*24.0*	*1.03 (0.961)*	*0.962*	*0.32-3.31*	*18.1*	*16.7*	*0.79 (0.755)*	*0.698*	*0.19-3.38*	*17.8*	*22.2*	*1.48 (0.681)*	*0.555*	*0.23-9.65*

*Table Interpretation: The variables listed are the comparison group. This means that the percentages reported are the percentages in the comparison group that either did or did not experience an event. Regarding the odds ratio (OR), an OR>1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. For example, as reported above, of those who *had not* experienced a general accident in the last 12 months, 44.3% had 'mental health problems', for those who *had* experienced an accident, 66.7% had 'mental health problems'. Those who had 'mental health problems' were 2.51 times more like to experience an accident than those who did not. [a]SF-12 Physical Component Score, [b]SF-12 Mental Component Score, [c]Kessler-10, [d]Alcohol Use Disorders Identification Test-C, [e]Over-the-counter, [f]In the benzodiazepine chronicity category, the chronic benzodiazepine group was used as the reference category and the intermittent and short-term groups were compared to this. [g]A monthly benzodiazepine (BZD) dose cut-off score of 300mg (diazepam equivalent) was used. This is equivalent to the defined daily dose of 10mg/day (World Health Organisation, 2011) being used daily for a month.

Table 6. *Univariate Logistic Regression Predicting Likelihood of Cognitive Failures*

	Prospective Memory (PM) Problems (Remembering to remember – e.g. an appointment, or to take medication) *n*=102					**Retrospective Memory (RM) Problems** (Remembering what you want to remember – e.g. forgetting information) *n*=99				
Predictor Variables Comparison Groups	**No PM problem % (*n*=82)**	**PM Problem % (*n*=20)**	**OR (significance)**	**Bootstrapped significance**	**95%CI**	**No RM Problem % (*n*=79)**	**RM Problem % (*n*=20)**	**OR (significance)**	**Bootstrapped significance**	**95%CI**
Demographic characteristics										
Age: ≥31 years	*69.5*	*45.0*	***0.36 (0.044)***	***0.051***	*0.13-0.97*	*67.1*	*55.0*	*0.60 (0.315)*	*0.341*	*0.22-1.63*
Male	*46.3*	*25.0*	***0.39 (0.090)***	***0.062***	*0.13-1.16*	*45.6*	*25.0*	***0.40 (0.102)***	***0.081***	*0.13-1.20*
Education:			*(0.537)*					*(0.466)*		
- University (baseline group)	*55.3*	*47.1*				*57.5*	*47.1*			
- Year 11/12 or Tafe/trade	*27.6*	*41.2*	*1.75 (0.337)*	*0.699*	*0.56-5.48*	*26.0*	*41.2*	*1.93 (0.261)*	*0.744*	*0.62-6.11*
- < Year 10	*17.1*	*11.8*	*0.81 (0.802)*	*0.283*	*0.15-4.29*	*16.4*	*11.8*	*0.88 (0.876)*	*0.267*	*0.16-4.68*
Income (<$13,000)	*46.1*	*47.4*	*1.05 (0.918)*	*0.910*	*0.39-2.89*	*44.6*	*55.6*	*1.55 (0.405)*	*0.393*	*0.55-4.38*
Unemployed	*41.5*	*57.9*	*1.94 (0.199)*	*0.181*	*0.71-5.34*	*39.2*	*68.4*	***3.36 (0.026)***	***0.013***	*1.15-9.76*
Unpartnered	*57.7*	*57.9*	*1.01 (0.987)*	*0.988*	*0.37-2.78*	*57.3*	*52.6*	*0.83 (0.712)*	*0.722*	*0.30-2.27*
Health factors										
Physical health Problems: PCS[a]	*11.5*	*10.5*	*0.90 (0.901)*	*0.755*	*0.18-4.56*	*12.0*	*10.5*	*0.86 (0.858)*	*0.734*	*0.17-4.37*
Mental health Problems: MCS[b]	*38.5*	*89.5*	***13.60 (0.001)***	***0.002***	*2.93-63.09*	*38.7*	*78.9*	***5.95 (0.004)***	***0.005***	*1.80-19.69*
Psychological Distress: K-10[c]	*44.2*	*83.3*	***6.32 (0.006)***	***0.008***	*1.69-23.64*	*43.2*	*82.4*	***6.13 (0.008)***	***0.002***	*1.62-23.14*
Chronic Health Conditions	*89.0*	*85.0*	*0.70 (0.618)*	*0.585*	*0.17-2.86*	*87.3*	*85.0*	*0.82 (0.782)*	*0.722*	*0.20-3.31*
Drug use										
Risky drinking: AUDIT-C[d]	*57.5*	*55.0*	*0.90 (0.840)*	*0.852*	*0.34-2.42*	*55.1*	*57.9*	*1.12 (0.828)*	*0.835*	*0.41-3.09*
Cannabis use	*33.3*	*26.3*	*0.71 (0.558)*	*0.582*	*0.23-2.20*	*30.7*	*36.8*	*1.32 (0.607)*	*0.602*	*0.46-3.78*
Other Illicit Drug Use	*25.3*	*21.1*	*0.79 (0.698)*	*0.692*	*0.23-2.65*	*23.7*	*26.3*	*1.15 (0.811)*	*0.825*	*0.36-3.63*
Antidepressant Use	*37.8*	*65.0*	***3.06 (0.032)***	***0.017***	*1.10-8.49*	*38.0*	*55.0*	*2.00 (0.172)*	*0.171*	*0.74-5.38*
Antipsychotic Use	*13.4*	*30.0*	***2.77 (0.082)***	***0.073***	*0.88-8.72*	*11.4*	*25.0*	***2.59 (0.128)***	***0.097***	*0.76-8.85*
Opioid Use	*30.5*	*25.0*	*0.76 (0.630)*	*0.635*	*0.25-2.32*	*29.1*	*30.0*	*1.04 (0.938)*	*0.939*	*0.36-3.05*
Other Psychotropic Use	*23.2*	*40.0*	*2.21 (0.132)*	*0.130*	*0.79-6.20*	*25.3*	*35.0*	*1.59 (0.387)*	*0.384*	*0.56-4.54*
OTC[e] Codeine Use	*59.5*	*36.8*	***0.40 (0.080)***	***0.078***	*0.14-1.12*	*57.9*	*42.1*	*0.53 (0.220)*	*0.218*	*0.19-1.46*
Prescribed painkillers	*34.2*	*36.8*	*1.12 (0.827)*	*0.825*	*0.40-3.18*	*31.6*	*47.4*	*1.95 (0.200)*	*0.220*	*0.70-5.42*
Monthly BZD Dose: >300mg[g]	*27.3*	*47.4*	***2.40 (0.096)***	***0.094***	*0.86-6.73*	*30.7*	*31.6*	*1.04 (0.939)*	*0.936*	*0.35-3.09*
Benzodiazepine Chronicity:[f]			***(0.041)***					***(0.020)***		
- Chronic Use (baseline group)	*34.1*	*65..0*				*32.9*	*60.0*			
- Intermittent Use	*50.0*	*20.0*	***0.21 (0.012)***	***0.006***	*0.06-0.71*	*53.2*	*15*	***0.16 (0.007)***	***0.003***	*0.04-0.60*
- Short-term	*15.9*	*15.0*	*0.50 (0.334)*	*0.279*	*0.12-2.05*	*13.9*	*25.0*	*0.99 (0.981)*	*0.987*	*0.28-3.47*

*Table Interpretation: The variables listed are the comparison group. This means that the percentages reported are the percentages in the comparison group that either did or did not experience an event. Regarding the odds ratio (OR), an OR>1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. For example, as reported above, of those who *had not* experienced prospective memory problems, 38.5% had 'mental health problems', for those who *had* experienced a prospective memory problems, 89.5% had 'mental health problems'. Those who had 'mental health problems' were 13.6 times more like to experience a prospective memory problems than those who did not. [a]SF-12 Physical Component Score, [b]SF-12 Mental Component Score, [c]Kessler-10, [d]Alcohol Use Disorders Identification Test-C, [e]Over-the-counter, [f]In the benzodiazepine chronicity category, the chronic benzodiazepine group was used as the reference category and the intermittent and short-term groups were compared to this. [g]A monthly benzodiazepine (BZD) dose cut-off score of 300mg (diazepam equivalent) was used. This is equivalent to the defined daily dose of 10mg/day (World Health Organisation, 2011) being used daily for a month.

Table 7. *Multivariate Logistic Regression Predicting Likelihood of Traffic Incidents*

Model	Traffic Accident Ever (*n*=78)			Traffic Accident – 12 months (*n*=78)			Traffic Near Misses (*n*=78)		
Comparison Groups	**OR**	***p***	**95%CI**	**OR**	***p***	**95%CI**	**OR**	***p***	**95%CI**
Step 1	*R^2=0.074*			*R^2=0.112*			*R^2=0.023*		
Chronic Use (baseline group):		*0.118*			*0.549*			*0.518*	
- Intermittent Use	**2.33**	***0.096***	0.86-6.29	0.47	*0.274*	0.12-1.83	1.20	*0.726*	0.43-3.39
- Short-term	0.71	*0.632*	0.17-2.90	0.00	*0.999*	-	2.22	*0.256*	0.56-8.81
Step 2	*R^2=0.185*			*R^2=0.253*			*R^2=0.445*		
Chronic Use (baseline group):		*0.217*			*0.356*			*0.858*	
- Intermittent Use	2.06	*0.179*	0.72-5.90	0.33	*0.151*	0.08-1.49	0.98	*0.973*	0.27-3.55
- Short-term	0.68	*0.621*	0.15-3.14	0.00	*0.999*	-	1.56	*0.624*	0.26-9.35
Step 3	*R^2=0.240*			*R^2=0.337*			R^2=0.480		
Chronic Use (baseline group):		***0.091***			*0.554*			*0.955*	
- Intermittent Use	***2.72***	***0.084***	*0.87-8.47*	0.42	*0.277*	0.09-2.02	1.19	*0.804*	0.31-4.59
- Short-term	*0.57*	*0.488*	*0.11-2.81*	0.00	*0.998*	-	1.27	*0.799*	0.20-7.94
Step 4	*R^2=0.348*			*R^2=0.618*			*R^2=0.612*		
Chronic Use (baseline group):		***0.052***			*0.919*			*0.760*	
- Intermittent Use	**4.24**	***0.037***	1.09-16.48	2.03	*0.681*	0.03-3.35	0.51	*0.464*	0.09-3.07
- Short-term	0.81	*0.829*	0.12-5.62	0.00	*0.998*	-	0.57	*0.669*	0.04-7.66
Age: ≥31 years	0.53	*0.341*	0.14-1.96	0.32	*0.341*	0.07-60.15	**0.12**	***0.012***	0.02-0.63
Male	1.59	*0.502*	0.41-6.20	0.29	*0.502*	0.01-11.09	**0.01**	***0.003***	0.00-0.22
Unemployed	**0.12**	***0.003***	0.03-0.49	5.39	*0.421*	0.09-325.79	**6.12**	***0.081***	0.80-46.86
Unpartnered	1.63	*0.434*	0.48-5.56	41.25	*0.121*	0.38-4531.29	**11.14**	***0.011***	1.75-70.77
Physical health Problems: PCS[a]	1.38	*0.760*	0.17-10.99	0.00	*0.998*	-	0.75	*0.829*	0.06-9.91
Psychological Distress: K-10[b]	2.49	*0.210*	0.60-10.40	0.07	*0.254*	0.00-7.02	2.98	*0.218*	0.52-16.95
Risky drinking (AUDIT-C)[c]	0.48	*0.289*	0.13-1.85	0.65	*0.780*	0.03-13.34	4.56	*0.136*	0.62-33.59
Cannabis use	0.81	*0.802*	0.15-4.31	0.04	*0.199*	0.00-5.66	3.34	*0.326*	0.30-37.02
Other Illicit Drug Use	0.86	*0.886*	0.11-6.56	113.80	*0.158*	0.16-80779.52	7.17	*0.151*	0.49-105.67
Antidepressant Use	1.20	*0.778*	0.33-4.37	88.15	*0.105*	0.39-19901.85	1.71	*0.527*	0.33-8.98
Antipsychotic Use	**5.37**	***0.057***	0.95-30.20	6.07	*0.350*	0.14-265.19	0.98	*0.980*	0.15-6.36
Opioid Use	1.47	*0.598*	0.35-6.22	82.03	*0.133*	0.26-25710.51	0.38	*0.318*	0.06-2.53
Other Psychotropic Use	**0.17**	***0.037***	0.03-0.90	**0.01**	***0.023***	0.00-0.54	3.59	*0.187*	0.54-24.07
OTC[d] Codeine Use	1.71	*0.395*	0.50-5.85	0.16	*0.263*	0.01-3.92	0.68	*0.674*	0.11-4.15
Monthly BZD Dose: >300mg[e]	1.08	*0.919*	0.23-5.07	4.18	*0.410*	0.14-126.05	0.19	*0.169*	0.02-2.02

*Table Interpretation: An odds ratio (OR) >1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. Model 1 included the benzodiazepine chronicity variable only. Model 2 added the variables: age, sex, employment, partnered. Model 3 added the variables: SF-12 physical component score, Kessler-10. Model 4 added the variables: AUDIT-C, cannabis use, other illicit drug use, antidepressant use, antipsychotic use, opioid use, other psychotropic use, over-the-counter codeine use, and monthly benzodiazepine dose. The *Nagelkerke R2* value indicates the amount of variance explained by the model. [a]SF-12 Physical Component Score, [b]Kessler-10, [c]Alcohol Use Disorders Identification Test-C, [d]Over-the-counter, [e]A monthly benzodiazepine (BZD) dose cut-off score of 300mg (diazepam equivalent) was used. This is equivalent to the defined daily dose of 10mg/day (World Health Organisation, 2011) being used daily for a month.

Table 8. Multivariate Logistic Regression Predicting Likelihood of *General Incidents*

Model Comparison Groups	**General Accident (*n*=80)**			**Frequent Injury_12m (*n*=82)**		
	OR	***p***	**95%CI**	**OR**	***p***	**95%CI**
Step 1	*R^2=0.082*			*R^2=0.012*		
Chronic Use (baseline group):		*0.150*			*0.737*	
- Intermittent Use	**0.29**	***0.059***	0.08-1.05	1.01	*0.985*	0.28-3.69
- Short-term	0.92	*0.912*	0.20-4.26	1.80	*0.476*	0.36-9.08
Step 2	*R^2=0.318*			*R^2=0.277*		
Chronic Use (baseline group):		*0.065*			*0.850*	
- Intermittent Use	**0.16**	***0.019***	0.04-0.74	0.77	*0.723*	0.18-3.28
- Short-term	0.39	*0.319*	0.06-2.48	1.270	*0.804*	0.19-8.42
Step 3	*R^2=0.381*			*R^2=0.366*		
Chronic Use (baseline group):		*0.106*			*0.994*	
- Intermittent Use	***0.18***	***0.039***	*0.03-0.91*	1.05	*0.948*	0.23-4.91
- Short-term	*0.26*	*0.197*	*0.03-2.03*	0.942	*0.955*	0.12-7.43
Step 4	*R^2=0.687*			*R^2=0.502*		
Chronic Use (baseline group):		*0.121*			*0.787*	
- Intermittent Use	**0.01**	***0.046***	0.00-0.933	0.47	*0.489*	0.05-4.03
- Short-term	0.05	*0.271*	0.00-10.34	0.57	*0.721*	0.03-12.81
Age: ≥31 years	**0.00**	***0.049***	0.00-0.97	**0.10**	***0.048***	0.01-0.98
Male	1.63	*0.719*	0.12-22.86	0.19	*0.123*	0.02-1.57
Unemployed	1.64	*0.688*	0.15-18.41	0.23	*0.150*	0.03-1.70
Unpartnered	**45.18**	***0.077***	0.66-3084.31	6.95	*0.115*	0.62-77.54
Physical health Problems: PCS[a]	0.20	*0.494*	0.00-21.03	0.00	*0.999*	-
Psychological Distress: K-10[b]	3.55	*0.499*	0.09-139.52	2.58	*0.423*	0.25-26.37
Risky drinking (AUDIT-C)[c]	0.18	*0.355*	0.00-7.94	0.51	*0.507*	0.07-3.79
Cannabis use	0.04	*0.147*	0.00-3.19	0.35	*0.573*	0.01-14.01
Other Illicit Drug Use	55.22	*0.149*	0.24-12828.60	5.71	*0.413*	0.09-371.53
Antidepressant Use	1.36	*0.813*	0.11-17.29	0.46	*0.398*	0.08-2.801
Antipsychotic Use	**554.46**	***0.011***	4.19-73392.64	6.70	*0.111*	0.64-69.75
Opioid Use	6.632	*0.224*	0.31-140.37	0.64	*0.698*	0.07-6.18
Other Psychotropic Use	**0.01**	***0.055***	0.00-1.12	2.35	*0.383*	0.35-15.91
OTC[d] Codeine Use	**9.48**	***0.097***	0.66-135.19	0.69	*0.662*	0.13-3.71
Monthly BZD Dose: >300mg[e]	0.16	*0.252*	0.01-3.779	0.56	*0.630*	0.05-5.97

*Table Interpretation: The predictor variables listed are the comparison group. This means that the percentages reported are the percentages in the comparison group that either did or did not experience an event. Regarding the odds ratio (OR), an OR>1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. The *Nagelkerke R2* value indicates the amount of variance explained by the model. [a]SF-12 Physical Component Score, [b]Kessler-10, [c]Alcohol Use Disorders Identification Test-C, [d]Over-the-counter, [e]A monthly benzodiazepine (BZD) dose cut-off score of 300mg (diazepam equivalent) was used. This is equivalent to the defined daily dose of 10mg/day (World Health Organisation, 2011) being used daily for a month. Note: Due to the small number of frequent minor injuries occurring in the last one month, there was overfit in the data and the model would not appropriately converge, therefore this data is not reported here.

Table 9. *Multivariate Logistic Regression Predicting Likelihood of Cognitive Failures*

Model Comparison Groups	Prospective Memory Problems (*n*=79)			Retrospective Memory Problems (*n*=76)		
	OR	***p***	**95%CI**	**OR**	***p***	**95%CI**
Step 1	*R^2=0.121*			*R^2=0.246*		
Chronic Use (baseline group):		***0.074***			***0.033***	
- Intermittent Use	**0.20**	***0.024***	0.05-0.81	**0.07**	***0.014***	0.01-0.58
- Short-term	0.83	*0.804*	0.18-3.78	1.33	*0.698*	0.31-5.72
Step 2	*R^2=0.319*			*R^2=0.468*		
Chronic Use (baseline group):		*0.066*			***0.036***	
- Intermittent Use	**0.15**	***0.020***	0.03-0.74	**0.06**	***0.014***	0.01-0.56
- Short-term	0.38	*0.315*	0.06-2.51	1.21	*0.845*	0.17-8.47
Step 3	*R^2=0.402*			*R^2=0.525*		
Chronic Use (baseline group):		*0.134*			***0.083***	
- Intermittent Use	***0.18***	***0.055***	*0.03-1.04*	**0.06**	***0.033***	0.01-0.80
- Short-term	*0.24*	*0.196*	*0.03-2.09*	1.002	*0.998*	0.13-8.02
Step 4	*R^2=0.593*			*R^2=0.750*		
Chronic Use (baseline group):		*0.396*			*0.229*	
- Intermittent Use	0.20	*0.178*	0.02-2.08	**0.01**	***0.091***	0.00-2.54
- Short-term	0.44	*0.619*	0.02-11.53	0.03	*0.347*	0.00-42.28
Age: ≥31 years	**0.04**	***0.026***	0.01-0.69	0.22	*0.358*	0.01-5.53
Male	0.21	*0.131*	0.03-1.60	**0.00**	***0.098***	0.00-3.55
Unemployed	7.05	*0.123*	0.59-84.52	**298.21**	***0.041***	1.26-70801.71
Unpartnered	0.33	*0.277*	0.05-2.42	0.15	*0.344*	0.00-7.78
Physical health Problems: PCS[a]	0.34	*0.564*	0.01-13.51	2.06	*0.807*	0.01-689.22
Psychological Distress: K-10[b]	4.35	*0.228*	0.40-47.64	13.63	*0.105*	0.58-319.21
Risky drinking (AUDIT-C)[c]	1.88	*0.571*	0.21-16.57	59.62	*0.245*	0.06-58755.97
Cannabis use	0.26	*0.425*	0.01-7.01	0.70	*0.921*	0.00-741.49
Other Illicit Drug Use	0.55	*0.735*	0.02-17.82	34.68	0.454	0.00-370397.75
Antidepressant Use	1.00	*0.999*	0.14-7.17	0.04	0.217	0.00-7.04
Antipsychotic Use	6.23	*0.135*	0.56-68.87	6.11	0.487	0.04-1001.82
Opioid Use	0.92	*0.942*	0.09-9.53	**30.22**	**0.095**	0.55-1648.71
Other Psychotropic Use	2.92	*0.334*	0.33-25.56	0.42	0.669	0.01-23.09
OTC[d] Codeine Use	**0.11**	***0.028***	0.02-0.79	0.01	0.124	0.00-3.22
Monthly BZD Dose: >300mg[e]	4.02	*0.282*	0.32-50.68	0.09	0.437	0.00-42.37

*Table Interpretation: The predictor variables listed are the comparison group. This means that the percentages reported are the percentages in the comparison group that either did or did not experience an event. Regarding the odds ratio (OR), an OR>1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. The *Nagelkerke R2* value indicates the amount of variance explained by the model. [a]SF-12 Physical Component Score, [b]Kessler-10, [c]Alcohol Use Disorders Identification Test-C, [d]Over-the-counter, [e]A monthly benzodiazepine (BZD) dose cut-off score of 300mg (diazepam equivalent) was used. This is equivalent to the defined daily dose of 10mg/day (World Health Organisation, 2011) being used daily for a month.

DISCUSSION

The patterns of benzodiazepine consumption found in this study are indicative of prolonged and frequent use. Chronic benzodiazepine use was associated with an increased risk of general accidents, and retrospective and prospective memory problems. Those who used most days for a year or more, experienced more of these problems, than those who used only sporadically over a similar time period. This may indicate that tolerance does not develop in chronic users as is often expected. Those who had a high monthly dose of benzodiazepines reported increased traffic accidents in the last 12 months.

The typical patterns of benzodiazepine use identified by many of this sample are far in excess of the clinical guidelines that recommend a time- and dose-limited approach. The short-term user group in this study were the most benzodiazepine-naïve participants. Whilst average dosage in the short-term group was within the defined daily dose (World Health Organisation, 2011), their average length of use spanned almost six months. The focus group of this study, the chronic users, had even higher levels of benzodiazepine use. Average length of use spanned almost nine years, and the average monthly dosage was 900mg diazepam equivalent – which is three times the monthly dose calculated using a defined daily dose. Use of more than one benzodiazepine was also common.

Incident rates in this sample were compared to the rates found in other general population research. Comparable research in the UK (Wadsworth et al., 2005) used a postal survey (n=7979) to examine psychotropic medication use in the general population, and found 11% of the population reported a general accident (excluding traffic accidents). In the current study, general accidents were reported by 22.94%, a significantly larger proportion of the population ($\chi^2(1_{n=8108})=17.03$, $p<0.001$). Experience of frequent minor injuries did not differ significantly between the populations, with rates of 14% in the UK, and 16% in the current study ($\chi^2(1_{n=8108})=0.30$, $p=0.587$). In this study, chronic users were three times more likely to experience a general accident requiring medical attention, in the last 12 months,

than intermittent users, and this finding remained in the multivariate results. This is a serious impact on the safety of this group.

Regarding traffic incidents whilst the driver, 50.87% of study participants had experienced an accident at any time in their life, and 14.91%, had experienced at least one in the last 12 months. 'Close calls' whilst driving were reported by 38.60% of the group. There is little available population data about rates of traffic incidents available for comparison. Most data is that collected from fatalities, or those requiring police or medical services, and does not capture more minor non-reported incidents. There was an association between lifetime experience of traffic accidents, and intermittent benzodiazepine use; this was the only variable for which the intermittent users were at higher risk than the daily users. However, there are limitations inherent in this comparison, as the predictor variables do not occur over this same 'lifetime' time frame. Those on a monthly dose of greater than 300mg (diazepam equivalent) were three times more likely to report having a traffic accident in the last 12 months, compared to those using less than 300mg (although this effect did not remain in the multivariate analysis). This finding supports the premise of using the lowest dose possible in order to reduce side-effects.

Expected cognitive performance was estimated for the Prospective Retrospective Memory Questionnaire using a large sample (*n*=551; Crawford & Smith, 2003). Assuming a standard distribution, approximately 16% of the general population is expected to score greater than one standard deviation above the mean. Proportions of the sample scoring greater than one standard deviation above the mean in this benzodiazepine sample were higher, but not significantly so, for both prospective memory (19.61%; χ^2 ($1_{n=680}$) =0.74, *p*=0.390) and retrospective memory (22.47%; χ^2 ($1_{n=680}$) =2.63, *p*=0.105). In this group, chronic benzodiazepine use and a high monthly dose were significantly associated with prospective memory problems in the univariate analysis, but this finding disappeared in the multivariate analysis, after controlling for demographic, health and drug use variables. Daily chronic users were at a higher risk of retrospective memory problems than occasional users, in both the univariate and multivariate analyses. Whilst the association between

memory deficits and benzodiazepine use is well established in the literature, this is the first study, to our knowledge, that has examined the relationship between prospective memory problems and chronic benzodiazepine use.

With the exception of lifetime traffic accidents, the chronic user group had an increased experience of incidents compared to the intermittent users. No significant differences were found between the short-term user group and the chronic group. The short-term group included all participants who identified they had used benzodiazepines for less than a year, and use was evenly split between daily (*n*=13, 54.2%) or occasional consumption (*n*=11, 45.8%). For those in the short-term and intermittent user groups who are occasional users of benzodiazepines, there may be some susceptibility to the acute effects of benzodiazepines each time they recommence use. However, as evidenced by the findings in this study, the chronic users experienced the greatest deficit. This is consistent with the literature suggesting tolerance to the effects of benzodiazepines does not develop equally, and for some functions may not occur at all (Vinkers & Olivier, 2012). This study suggests that psychomotor deficits build as the duration and frequency of benzodiazepine use increases, and does not lessen through the development of tolerance to particular features of benzodiazepines.

There were also other predictors that emerged regularly in the analyses. Due to the exacerbated effects of benzodiazepines on older adults (Barker et al., 2004a), the older age group was expected to be at greatest risk of incidents. However, stronger associations were found between most incident types and being in the younger age group (average age=25.19 years, *SD*=3.81), compared to being in the older adult group (average age=45.57 years, *SD*=11.18). It is possible that the association with incidents may change if a group of much older adults, for example with an average age of 70, were included. Being female, unemployed, and the use of various sedating medications appeared to have independent effects on increasing risk of incidents. Overall, there are some complexities to the pattern of predictors in this study. Larger participant numbers may have allowed these trends to become more obvious. The influence of these extraneous variables on the results support the

methodology used in this study which controls for a range of other demographic, health, and drug use factors.

Unfortunately despite varied methods of participant recruitment, data obtained were less than expected, which affected the power of the study. It is unclear why the response rate for this survey remained low, despite various different methods of recruitment. It is thought that the low completion rate may be in part due to the lengthy survey. The small sample size meant the individual effects of different active ingredients could not be explored as planned. It remains an ongoing limitation in the literature to date that most studies do not differentiate between benzodiazepine types, despite the varied differences in potency and half-life between the individual preparations. The use of diazepam equivalent doses goes some way towards resolving this. The fact that effects have remained, despite this small sample size, points to the severity of the effects of these medications and the magnitude of the issue in the general population.

The use of a survey in this study involves a reliance on self-report, meaning incident reports may be prone to forgetfulness and under-reporting. Research suggests that more significant accidents are usually successfully recalled within a 12 month period; however, recall of more minor injuries may be diminished over a period greater than three months (Harel et al., 1994; Moshiro, Heuch, Astrom, Setel, & Kvale, 2005). It is possible there may be some type of recall bias occurring for the minor incidents, in which they are neither critical enough in severity nor frequent enough in occurrence to be accurately recalled. However, reported rates were similar to those found in other comparable populations, suggesting that either there has not been persistent under-reporting occurring in this sample, or that there is consistent recall bias with these types of studies. Another potential issue with the reporting of minor injuries is that the related survey questions were non-definitive and left the decision of what constituted a minor injury and how frequently they occurred, to the judgement of respondents. Comparatively major accidents were more clearly defined by the requirement of medical attention. Nevertheless, minor injuries have the potential to have a cumulative impact on a

person's wellbeing, and are worthy of further study. Future research could focus on more specific prompts regarding minor injuries, and use real-time technology, such as a Phone App to capture individual's experiences as they occur.

Accountable prescribing is described as "the use of medicines with proven effectiveness and the avoidance of medicines when they do not help or cause harm" (Morden, Schwartz, Fisher, & Woloshin 2013; Royal Australian College of General Practitioners, 2015a: p.18). Whether the benzodiazepine use within this sample aligns with these principles is unclear. For example, almost half the group stated they use benzodiazepines to treat anxiety, yet average Kessler-10 (Kessler & Mroczek, 1994) scores were indicative that high anxiety and affective symptoms remain. Similarly, the SF-12 mental component score (Ware et al., 1995), which indicates the effect of mental health on social and emotional functioning was on average close to 2 standard deviations below the mean, suggesting a lower than average wellbeing. Prescribers need to continually balance the ongoing clinical efficacy, with the potential negative effects, such as the detrimental impact on safety identified in this study. Given that most of the sample identified that they were using benzodiazepines for sleep only (*n*=59, 45.7%) or anxiety only (*n*=54, 41.9%), it is expected that there should be other medications and therapies that would be preferable first-line treatments, due to their higher efficacy and lower risk of side-effects, particularly for ongoing use (Baldwin et al., 2013; National Institute for Health and Care Excellence, 2014).

There are several clinical recommendations that arise from this study. Results support the premise that complete tolerance does not occur in chronic users. For prescribers, this means that even long-term benzodiazepine users should be regularly cautioned about detrimental safety effects. Awareness of ongoing risks to safety, and the subsequent actions required to mitigate risk, for example refraining from driving, may provide motivation for patients to cease use. An association was found between higher doses of benzodiazepines, and increased accidents. This evidence can be used as a 'selling point' to patients about the benefits of a reduction in dose. Finally, it is apparent that there must be some method for

identifying long-term benzodiazepine users, and providing them with alternative solutions for managing their concerns, whether this is a pharmacological or psychological treatment.

Current clinical guidelines suggest that benzodiazepines should be used at the lowest effective dose for the shortest time period possible, with use for longer than four weeks rarely warranted (Royal Australian College of General Practitioners, 2015b). The first clinical guideline suggesting this limited use of benzodiazepines was implemented in the UK in the 1980s (Committee on the Review of Medicines, 1980), and since then many international guidelines have followed. However, over 35 years on, patterns of benzodiazepine use found in the current study are far from that recommended. Many individuals had use spanning several years, high daily doses, and used multiple benzodiazepine types. It is highly unlikely that such high levels of use are justified in the vast majority of this group. It could be readily assumed that the chronic benzodiazepine users in this study, who have had many years of ongoing use, would be less susceptible to the impairing effects of benzodiazepines. However, results suggest that full tolerance does not develop to incident risk, with chronic users at a greater risk of general accidents, and prospective and retrospective memory problems, compared to those who use only intermittently. The association between chronic benzodiazepine use and accidents remained, even after controlling for other demographic, health and drug use variables, which indicates the strength of this association. Data from this study suggests the effects of benzodiazepines on safety cannot be ignored. There must be continual assessments made as to whether the ongoing use of benzodiazepines is indicated, with careful consideration given to costs and benefits. Both prescribers and patients must be provided with adequate skills to cease benzodiazepine use, and to find alternative solutions.

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7 The Unique Impact of Benzodiazepines on the Safety of People Who Inject Drugs

CHAPTER 7: THE UNIQUE IMPACT OF BENZODIAZEPINES ON THE SAFETY OF PEOPLE WHO INJECT DRUGS

Preface

Study 1 examined the association between chronic benzodiazepine use and accidents in the general population. It was found that benzodiazepine use in the sample investigated was ongoing and regular, and there was a higher rate of safety incidents experienced by the most chronic user group. The focus of this chapter is similar to that of *Study 1*, in that it examines the association between benzodiazepine use and experience of accidents; comparable methodology and data analysis was used. However, *Study 2* specifically examines this association within a high-risk population – people who inject drugs (PWID). PWID are already a high risk group, due to both their typical population demographics, and common risk-taking behaviours. *Study 2* aimed to understand whether benzodiazepines uniquely contributed to risk of safety incidents in people who inject drugs *(Research Question 3).* Data for this study comes from the Tasmanian Illicit Drug Reporting System (IDRS), and was collected during 2009 and 2010. The author acknowledges the work of those involved in the IDRS in collecting and collating the data. It is hoped that the results will improve the understanding of the risks faced by those who are polydrug users, and contribute to harm minimisation knowledge.

ABSTRACT

Objective

The use of benzodiazepines in people who inject drugs (PWID) is usually counter indicated, due to the high risk of dependence, respiratory depression, and other adverse events. Despite this it is known that PWID commonly use benzodiazepines, both for their own and synergistic effects, and for managing withdrawal from other substances. The current study aimed to examine whether benzodiazepines independently contributed to risk of safety incidents in PWID. Specifically three incident types were examined; cognitive failures, minor injuries, and accidents requiring medical attention.

Method

170 participants were interviewed through the Illicit Drug Reporting System. Data was collected in Hobart, Tasmania, in 2009 and 2010. Participants were required to be over 18 years of age, and to have injected drugs within the last six months.

Results

After controlling for other confounding variables, moderate-to-regular benzodiazepine use independently contributed to an increased risk of retrospective memory problems (Multivariate OR 8.21, 95%CI 1.03-65.41, p=0.047), and major accidents (Multivariate OR 3.88, 95%CI 1.20-12.50, p=0.023).

Conclusion

Reported rates of safety incidents were elevated in this sample compared to the general population. Despite the extensive injecting drug use in this group, benzodiazepine use had an independent and detrimental effect on the safety of the cohort. This suggests that benzodiazepines cannot be ignored as a target for harm minimisation in this group.

INTRODUCTION

There is a large body of evidence supporting a relationship between benzodiazepines, commonly used for sleep and anxiety, and psychomotor impairment. There are significant cognitive effects during early benzodiazepine use, such as sedation, memory problems, and motor impairment (Buffett-Jerrott & Stewart, 2002. De Visser et al., 2002). Long-term benzodiazepine users also show a generalised deficit across a broad range of cognitive areas (Barker, Greenwood, Jackson, & Crowe, 2004a, 2004b, 2005). As a class, prescribing of benzodiazepines in Australia appears to have stabilised (Stephenson, Karange, & McGregor, 2013); however, around 7 million scripts are still written every year and research suggests that quantity per script may be increasing (Islam, Conigrave, Day, Nguyen, & Haber, 2013).

The effects of long-term benzodiazepine use on cognition, has been investigated in a meta-analysis of 13 studies (Barkeret al., 2004a). The benzodiazepine user group had benzodiazepine use varying between 1-34 years, with a mean duration of 9.9 years. In 11 out of the 13 studies a control group was used, including people classified as; non-anxious, anxious, and previous benzodiazepine users. The current benzodiazepine users were significantly impaired across all 12 cognitive domains studied (cognitive domains: sensory processing, psychomotor speed, nonverbal memory, visuospatial, attention/concentration, speed of processing, general intelligence, working memory, problem-solving, verbal memory, motor control/performance and verbal reasoning). Moderate to large effect sizes were found for all cognitive domains; the mean weighted effect size was -0.74 (SD±0.25) and no 95% confidence interval spanned zero, meaning results are statistically significant.

These well-established laboratory findings are substantiated by the high rates of benzodiazepine users in road (Dassanayake, Michie, Carter, & Jones, 2011; Kelly, Darke, & Ross, 2004), work (Wadsworth, Moss, Simpson, & Smith, 2005) and other accidents (Stenbacka, Jansson, Leifman, & Romelsjö, 2002). A review of

epidemiological traffic data by Kelly, Darke, and Ross (2004) found that following cannabis, benzodiazepines were the most commonly detected drug in drivers involved in an accident and apprehended for impaired driving. A recent meta-analysis (Dassanayake et al., 2011) found that people who used benzodiazepines were 60-80% more likely to be involved in accidents (for case-control studies: 59%, pooled OR 1.59; 95%CI 1.10-2.31, and for cohort studies: 81% pooled incidence rate ratio 1.81; 95%CI 1.35-2.43), and importantly were 40% more likely to be 'responsible' for the accident (pooled OR 1.41; 95%CI 1.03, 1.94).

In a randomised general population postal survey in the United Kingdom, Wadsworth, Moss, Simpson and Smith (2005), investigated the effects of psychotropic medication use on respondents' experience with major accidents, minor injuries and cognitive failures (minor everyday cognitive slips or errors). Initial analysis found a significant association between benzodiazepine use and non-work injuries, with benzodiazepine users almost four and a half times more likely to experience a non-work injury (OR 4.43, 95%CI 1.89-10.38). To further clarify findings, participants were classified by mental health status and according to low or high presence of other risk factors associated with the incident type, such as physical health, age, and risk-taking. In the presence of high risk factors, and a mental health condition, benzodiazepine use markedly increased the risk of non-work injuries (OR 16.18, 95%CI 6.24-41.94) and cognitive failures (OR 18.09, 95%CI 6.17-53.04). This approach by Wadsworth and colleagues is unique in its exploration of a range of incident severities, previously research has focused mostly on accidents requiring medical attention.

Cognitive failure is a broad term used to define problems of memory, attention, or action. Cognitive failures are common and usually benign, but can have serious consequences (Wallace, Kass, & Stanny, 2002). They normally reflect a failure of typical functioning rather than a lack of ability (Wallace et al., 2002). Prospective memory (remembering to perform a future event) and retrospective memory (remembering previously learned information) are processes prone to cognitive failures. Whilst these types of memory are distinct concepts, they interact in the

everyday memory required to live independently (Crawford & Smith, 2003). For example the simple task of planning to call a colleague, requires both prospective memory (remembering to call at the appropriate time) and retrospective memory (remembering what you needed to discuss).

The impact of benzodiazepines on memory is highly researched; whilst a general detrimental effect occurs, the many types of memory processes are differentially affected by benzodiazepines (Barker, Jackson, Greenwood, & Crowe, 2003; Rich, Svoboda, & Brown, 2006). Retrospective and prospective memory impairment has been established in self-report and lab-based objective measures in users of alcohol (Griffiths et al., 2012), nicotine (Heffernan et al., 2005), cannabis (Bartholomew, Holroyd, & Heffernan, 2010; Montgomery, Seddon, Fisk, Murphy, & Jansari, 2012), ecstasy (Rendell, Gray, Henry, & Tolan, 2007), cocaine (Hadjiefhyvoulou, Fisk, Montgomery, & Bridges, 2011), methamphetamines (Rendell, Mazur, & Henry, 2009) and opiate maintenance drugs: methadone, buprenorphine and suboxone (Terrett et al., 2014). Experimental studies examining retrospective memory through recall and recognition tasks, have established a dose- and time- dependent effect of acute use of benzodiazepines (Barker et al., 2003). An exploratory study, found that in healthy participants, a once-off weight-relative dose of diazepam impaired performance on both retrospective and prospective memory tasks (Rich et al., 2006). However, there have been few studies examining the relationship between ongoing benzodiazepine use and self-reported retrospective and prospective memory failures in the context of everyday life.

When considering demographic factors alone, the injecting-drug population has attributes commonly associated with increased experience of accidents and injuries, including for example; male sex, young age, low income, low education, and psychological distress (Simpson, Wadsworth, Moss, & Smith, 2005). Risk-taking behaviour is also a common trend in people who inject drugs (PWID), an observation supported by the findings of the 2013 Illicit Drug Reporting System (IDRS). In this national sample of 887 PWID, significant proportions of the sample identified that they undertook risky behaviours such as; sharing needles (11%) and

other injecting equipment (24%), being involved in criminal activity in the last month (36%), and of the 42% of the sample who had driven within the last 6 months, considerable numbers had driven under the influence of alcohol (18%) or an illicit drug (77%) (Stafford & Burns, 2014).

The sample for the current study was formed from the 2009 and 2010 Tasmanian IDRS samples. As such, the relevant IDRS reports provide an indication of the pattern of benzodiazepine and other drug use that occurs in the current sample. In the cohort of the 2009 IDRS (N=100; de Graaff & Bruno, 2010), the mean reported age of first injection was 18.9 years (SD=4.6, range 12-33). Regarding the 2009 cohort's drug of choice, 33% reported they preferred heroin, whilst 21% preferred methamphetamine. Consistent with this preference, 73% stated an opioid was the drug they had most often injected in the preceding month. Most (95%) of the 2009 IDRS sample had used benzodiazepines at some point in their lives; 51% of the sample had ever injected benzodiazepines, and 25% had injected in the six months prior to interview. Similar numbers in the cohort reported ever having been prescribed a benzodiazepine (78%, n=78), compared to lifetime use of illicit benzodiazepines (83%, n=83). Importantly, there was a large amount of overlap in the use of licit and illicit benzodiazepines. Out of those who had recently used benzodiazepines: 44% reported illicit benzodiazepine use only (n=34), 15% reported licit use only (n=12), and 41% had recently used benzodiazepines accessed both licitly and illicitly (n=32). The most common self-reported reasons for using benzodiazepines was self-treatment (48%, n=30), and intoxication purposes (37%, n=23). Overall, these findings suggest that PWID tend to use benzodiazepines in a risky manner; benzodiazepines are used regularly, and commonly in conjunction with other sedatives, and they are often injected, accessed from illicit sources, and used for non-clinical reasons. The safety of PWID is complicated due to demographic characteristics associated with adverse events, hazardous behaviour, and poly-drug use. It is assumed that the combined impact of these factors would make PWID very vulnerable to a range of incident types, including everyday cognitive failures, minor injuries, and major accidents requiring medical attention.

The aim of this study was to determine whether, within this complex context, benzodiazepines contribute any additional risk to PWID.

METHOD

Participants and Procedure

Data was collected as part of the Illicit Drug Reporting System, an Australian drug monitoring system. A total of 170 participants were recruited through a purposive sampling strategy in Hobart, Tasmania in June 2009 and 2010. Inclusion criteria required that participants be at least 18 years old, and had injected drugs at least monthly in the preceding six months. Trained staff conducted interviews with participants lasting 30-60 minutes in a range of public locations. Demographic characteristics, drug use, and health were assessed. Respondents provided written informed consent and were reimbursed AUD$40. For those who had completed the study in both years, 2010 data was omitted. Full methodological detail and findings are available elsewhere (de Graaff & Bruno, 2010; de Graaff & Bruno, 2011). Ethical approval was granted by the University of New South Wales and the Tasmanian Social Sciences Human Research Ethics Committee (approval H0007853 for the Tasmanian committee).

Outcome variables

Self-reported experiences of safety incidents were classified as major accidents or minor injuries. The number of major accidents experienced in the last 12 months was recorded; these being accidents that required medical attention, not resulting from assault. Those reporting one or more accidents were compared with those reporting none. Minor injuries, experienced in the last 12 months, included non-venous cuts and bruises that did not require medical attention. These were rated on a five-point frequency scale, ranging from ‘Not at all’ through to ‘Very frequently’. Those rating their experience of minor injuries as ‘quite’ or ‘very’ frequent, were compared to those who reported less frequent minor injuries. These questions

were replicated from the survey used by Wadsworth and colleagues (Wadsworth et al., 2005; Wadsworth, Simpson, Moss, & Smith, 2003).

Day-to-day cognitive failures were assessed using the Prospective and Retrospective Memory Questionnaire (PRMQ: Smith, Della Sala, Logie, & Maylor, 2000). The PRMQ has 16 items, split equally between those measuring prospective memory problems (e.g., *Do you decide to do something in a few minutes time and then forget to do it?*) and retrospective memory problems (e.g., *Do you forget something that you were told a few minutes before?*). Problems experienced in the last 6 months are rated on a 5 point scale ranging from 'never', to 'very often'. Higher scores are more indicative of memory problems. Confirmatory Factor Analysis of the PRMQ items indicates best fit for a three-factor model, with a general memory factor, and two orthogonal factors – prospective and retrospective memory (Crawford & Smith, 2003; Rönnlund, Mäntylä, & Nilsson, 2008). Crawford and Smith (2003) provide normative data based on a general adult UK population (*m*=38.88, *SD*=9.15), and using Cronbach's alpha indicated strong internal consistency for the PRMQ (prospective scale α=0.84, retrospective scale α=0.80 and total scale α=0.89). Problem scores were defined as a score ≥2*SD*s above the general population mean (approximately2.3% of the population). Problem scores for each measure were defined as follows: prospective memory ≥30, retrospective memory ≥28.65.

Measures

The predictor variables were chosen due to their known association with decreased safety and/or their potentially confounding nature (Table 1). Each of these variables were used as a categorical variable, with cut-off scores chosen to denote 'problem' versus 'non-problem' groups. This then allowed for the demarcation of a level at which an incident variable occurred, rather than simply providing information on the relationships between variables, as would have happened if the variables were treated in a continuous manner. For all drug types, use within the last 6 months was recorded, with daily users compared to those who used less than daily. The exception to this was amphetamines; due to low levels of daily use within the

population, comparisons were made between weekly and less than weekly users. To clarify findings, an additional graded benzodiazepine variable was included comparing those who used; less than weekly (low use), 1-6 times per week (moderate use), and most days each week (regular use).

The Kessler Psychological Distress Scale (K-10) is a 10-item questionnaire providing a global indication of anxiety and depression symptoms (Kessler & Mroczek, 1994). Symptoms experienced over the past four weeks are rated on a 5 point scale ranging from 'none of the time' to 'all of the time'. Whilst different cut-off scores are used within Australia, the convention set by the Australian Bureau of Statistics (2003) was followed, with total scores equal to or above 22, taken as an indication of high psychological distress. Andrews and Slade (Andrews & Slade, 2001) found that the K-10 appropriately identified those classified by the Composite International Diagnostic Interview v2.0, as having any DSM-IV or ICD-10 anxiety or affective diagnosis (at a score of 22; sensitivity=0.55, specificity=0.95).

The Personal Wellbeing Index (PWI) is designed to provide a subjective measure of quality of life (International Wellbeing Group, 2013). This scale is based on the premise that each person has a genetically determined 'set-point' for well-being that is internally maintained (Cummins et al., 2011). The PWI rates this set point on a standardised 0-100 point scale. Data for the average Australian wellbeing is collected regularly; there is minimal variation in the PWI score across each occasion of data collected (Cummins et al., 2011). The PWI has seven items each assessing a broad personal life domain, including – health, personal relationships, safety, standard of living, achieving, community connectedness, and future security. Ratings are made on a 10-point scale ranging from 'no satisfaction at all' through to 'completely satisfied'. It is suggested that a 'normal' range can be calculated based on 2 standard deviations either side of the mean (Cummins et al., 2011). In 2011, data was collected from 2000 randomly selected adults in a geographically representative Australian sample (Cummins et al., 2011). Based on this data (m=75.46, SD=12.87), the current study defines low quality of life as scores less than 49.72 (greater than $2SD$ below the mean).

The Short-Form Health Surveys are a group scales providing a general measure of self-rated health. Whilst the SF-36 has been extensively tested and used within Australia, the briefer form, the SF-8 was chosen for brevity, and was re-scaled to fit SF-36 norms. The SF-8 measures 8 domains, across the last four weeks; physical functioning, role functioning related to physical problems, bodily pain, general health, vitality, social functioning, role functioning related to emotional problems and mental health. These domains then combine to form a physical component summary score and mental component summary score. For each scale, scores range between 0-100, with higher scores equating to better health. Norms from a South Australian population study were chosen as the most up-to-date and representative Australian norms (Avery, Dal Grande, & Taylor, 2004). Those scoring less than two standard deviations below the mean were identified as the problem group, cut-off scores were as follows; physical component summary score ≤28.62 (norms; *m*=48.99, *SD*=10.18) and mental component summary score ≤34.79 (norms; *m*=52.38, *SD*=8.79).

In addition to the distinction made between people who consumed alcohol daily, or less than daily, problematic alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT; Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). The AUDIT is a 10-item questionnaire developed to identify risky or harmful drinking, as well as alcohol dependence. The AUDIT has demonstrated excellent psychometric characteristics, and has been validated in large multi-nation studies (de Meneses-Gaya, Zuardi, Loureiro, & Crippa, 2009). Scores range from 0-40, with higher scores indicative of more problematic alcohol use. Scores of 16 and above represent high levels of alcohol problems.

Table 1. *Rationale for inclusion of Predictor variables*

Factor:	Categorisation: *(at risk, low risk)*[a]	Included because of previous association with:
Age	0-30 years, 30 years plus	*Accidents* (Bureau of Infrastructure, 2014; Simpson et al., 2005; Wadsworth, Simpson, et al., 2003) *Injuries* (Simpson et al., 2005; Wadsworth, Moss, Simpson, & Smith, 2003; Wadsworth, Simpson, et al., 2003) *Cognitive failures* (Simpson et al., 2005; Wadsworth, Simpson, et al., 2003),
Sex	Male, female	*Accidents* (Bureau of Infrastructure, 2014; Simpson et al., 2005) *Injuries* (Pointer, 2013) *Cognitive failures* (Simpson et al., 2005),
Education	Grades 1-10, Grades 11-12[b]	*Accidents* (Cubbin & Smith, 2002) *Injuries* (Cubbin & Smith, 2002) *Cogniti*ve failures (Wadsworth, Simpson, et al., 2003; Weinborn, Woods, O'Toole, Kellogg, & Moyle, 2011),
Income (weekly)[c]	≤$504, >$505	*Accidents* (Cubbin & Smith, 2002) *Injuries* (Cubbin & Smith, 2002; Simpson et al., 2005), *Cognitive failures* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003; Wadsworth, Simpson, et al., 2003),
Employment Status	Not employed, Employed	*Accidents* (Australian Bureau of Statistics, 2011) *Injuries* (Simpson et al., 2005; Wadsworth, Simpson, et al., 2003) *Cognitive failures* (Simpson et al., 2005; Wadsworth, Simpson, et al., 2003),
Relationship Status	Partnered, Non-partnered	*Accidents* (Wadsworth, Moss, et al., 2003) *Injuries* (Wadsworth, Moss, et al., 2003)
Physical health problems	SF-8 Physical Component Score[d] cut-off ≤2SD population; ≤ 28.62, >28.63	*Accidents* (Simpson et al., 2005) *Injuries* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003) *Cognitive failures* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003)

Factor:	Categorisation: *(at risk, low risk)*[a]	Included because of previous association with:
Mental health problems	SF8 Mental Component Score[e] cut-off ≤2SD population; ≤34.79, >34.80 *and* Kessler-10[f] score 22-50, 0-21	*Accidents* (Hilton & Whiteford, 2010; Simpson et al., 2005) *Injuries* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003; Wadsworth, Simpson, et al., 2003) *Cognitive failures* (Simpson et al., 2005; Wadsworth, Moss, et al., 2003; Wadsworth, Simpson, et al., 2003)
Quality of Life	PWI[g] cut-off ≤2SD population; Scores ≤ 49.72, > 49.73	*Accidents* (Cummins et al., 2011) *Injuries* (Cummins et al., 2011) *Injecting drug use* (Dietze et al., 2010)
Alcohol Consumption	Daily Alcohol: Used 180 + times, Used 0-179 times (within 6 month period) *and* Risky drinking/AUDIT[h] score: 16-40, 0-15	*Accidents* (Bureau of Infrastructure, 2014; Movig et al., 2004; Simpson et al., 2005) *Injuries* (Burger, Lichtenstein, Hays, & Decker, 1990) *Cognitive failures* (Griffiths et al., 2012; Heffernan, Moss, & Ling, 2002)
Daily cannabis use	Used 180 + times, Used 0-179 times (within 6 month period)	*Accidents* (Kelly et al., 2004; Wadsworth, Moss, Simpson, & Smith, 2006) *Injuries* (Barrio et al., 2012; Wadsworth et al., 2006) *Cognitive failures* (Bartholomew et al., 2010; Matthews & Bruno, 2011; Montgomery et al., 2012)
Daily benzodiazepine use	Used 180 + times, Used 0-179 times (within 6 month period)	*Accidents* (Kelly et al., 2004; Movig et al., 2004) *Injuries* (Wadsworth et al., 2005) *Cognitive failures* (Barker, Greenwood, Jackson, & Crowe, 2004b; Rich et al., 2006; Wadsworth et al., 2005)
Graded Benzodiazepine use	Regular: Used 144-180, Moderate: Used 24-143 times, Low: Used 0-23 times (within 6 month period)	*Accidents* (Kelly et al., 2004; Movig et al., 2004) *Injuries* (Wadsworth et al., 2005) *Cognitive failures* (Barker, Greenwood, Jackson, & Crowe, 2004b; Rich et al., 2006; Wadsworth et al., 2005)

Factor:	Categorisation: *(at risk, low risk)*[a]	Included because of previous association with:
Daily opioid use	Used 180 + times, Used 0-179 times (within 6 month period)	*Accidents* (Hulse, English, Milne, & Holman, 1999; Kelly et al., 2004; Raes et al., 2008) *Injuries* (Majdzadeh et al., 2009) *Cognitive failures* (Terrett et al., 2014)
Weekly Amphetamine Use	Used 24-80 times, Used 0-23 times(within 6 month period)	*Accidents* (Kelly et al., 2004; Raes et al., 2008) *Cognitive failures* (Ludicello et al., 2011; Rendell et al., 2009)
Daily tobacco use	Used 180 + times, Used 0-179 times (within 6 month period)	*Accidents* (Wadsworth, Simpson, et al., 2003) *Injuries* (Collins & Lapsley, 2008; Wadsworth, Simpson, et al., 2003) *Cognitive failures* (Heffernan et al., 2005; Simpson et al., 2005)
Daily injection	Injected 180 + times, Injected 0-179 times (within 6 month period)	Dependence & drug related harms (Loxley et al., 2004)

[a]Predictor variables were used a categorical variables, and were separated into 'at risk' and 'low risk' groups, based on findings and cut-off scores from previous literature. In the regression analyses, the 'low risk' categories were the baseline group, and the 'at risk' categories were the comparison group. [b]In Australia, Grade 11 students are normally 16-17 years of age, and are typically in their twelfth year of education. [c]This weekly amount represents the poverty line for a single working adult. If the income for a family unit is less than the applicable poverty line, they are considered to be in poverty (Melbourne Institute of Applied Economic and Social Research, 2014). This amount does not take into account the presence of other dependent family members. [d]Short-Form Health Survey-8 – Physical Component Score (Ware, Kosinski, & Keller, 1995) [e]Short-Form Health Survey-8 – Mental Component Score (Ware, Kosinski, & Keller, 1995) [f]Kessler Psychological Distress Scale (K-10: Kessler & Mroczek, 1994). [g]Personal Wellbeing Index (International Wellbeing Group, 2013). [h]Alcohol Use Disorders Identification Test (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993).

Analysis

Using SPSS (Version 22) univariate logistic regression was conducted to examine associations between demographic, substance use, and health related predictor variables, and the dependent measures; major accidents, frequent minor injuries, prospective memory problems, and retrospective memory problems. The predictor variables were categorical, divided into 'at risk' or 'low risk' classifications. For each variable the 'low risk' group was used as the baseline group in the analysis, and the 'at risk' group was used as the comparison group. Therefore, an odds ratio of >1,

means that the outcome variable is more likely to occur in the comparison group compared to the baseline group. Given that the current sample size is small, the decision was made to also run a bootstrapping analysis. Bootstrapping is a general resampling procedure and was used to aid in interpretation of results. A multivariate model was then run, and to avoid multicollinearity the following variables were excluded; income, SF-8 Mental component, risky drinking (AUDIT), and daily benzodiazepine use. All other variables listed in Table 1 were included in the analysis. Data from this analysis is reported in the multivariate results. A final stepwise analysis was run in order to determine the individual contribution of benzodiazepine use to safety. Model 1 included demographic predictors only (age, sex, education, employment, partnered, physical health problems, psychological distress, and quality of life), Model 2 added drug use variables, excluding benzodiazepines (daily alcohol, daily cannabis, daily opioid, daily tobacco, weekly amphetamine, and daily injecting) and Model 3 added the graded benzodiazepine variable (low, moderate, and regular use).

RESULTS

Sample Characteristics

Participants (*n*=170) had a mean age of 33.91 years (*SD*=9.05, range 19-60) and 59.4% (95%CI 52.0-66.8) were males. Mean grade of school completion was grade 10 (*SD*=1.53, range grades 4-12), with slightly less than half (45.9%, 95%CI 38.4-53.4) completing further qualifications, and the majority being unemployed (74.7%, 95%CI 68.2-81.2). Respondents typically injected on multiple occasions per week (57.6%, 95%CI 50.2-65.0), with about one-third injecting daily (34.6%, 95%CI 27.5-41.8), despite this over half were not in substitution treatment (55.9%, 95%CI 48.4-63.4).

Logistic Regression

Results from the univariate analysis are shown in Tables 2 and 3, from the multivariate analysis in Table 4 and 5, and Table 6 presents the Nagelkerke R^2 values.

Major Accidents

A considerable 18% (95%CI 12.8-24.7) of this sample had experienced at least one accident requiring medical attention in the last 12 months. The only significant predictors of major accidents were physical health problems and regular benzodiazepine use (at least 6 times a week). There was a trend towards increased accidents for daily cannabis users. In the multivariate analysis, benzodiazepine use most days and daily opioid use were the only significant predictors of accidents. As shown by the stepwise analysis, benzodiazepines contributed independently to 5.4% of the variance in the model.

Minor Injuries

Minor injuries were experienced by 24.8% (95%CI 18.8-32.1%) of the sample. Those with low quality of life were almost three times more likely to report frequent minor injuries; this was the only significant association. There were trends close to significance for those who were unpartnered and used cannabis daily. After controlling for other factors in the multivariate model, the only predictor approaching significance was daily cannabis use.

Prospective Memory

Prospective memory problems were found in 22.2% (95%CI 16.4-29.2) of the sample. There were associations between prospective memory problems and regular benzodiazepine use, physical health problems, psychological distress, low quality of life, daily alcohol use, daily cannabis use, daily injecting, being female, and being partnered. After controlling for other variables in the multivariate model, those with physical health problems were almost 25 times more likely to experience

a prospective memory problem. Surprisingly, those with prospective memory problems were also significantly more likely to be employed, or have a partner. Daily cannabis use and weekly amphetamine use were also significant predictors of prospective memory problems. Stepwise analysis showed that benzodiazepine use did not contribute independently to the risk of prospective memory problems.

Retrospective Memory

In this group, 10.8% (95%CI 6.8-16.6) reported retrospective memory problems. The univariate analysis revealed those experiencing retrospective memory problems were significantly more likely to be female, report problems with physical and mental health, psychological distress, and low quality of life, and to consume alcohol daily, inject daily, and use benzodiazepines most days in a week. In the multivariate analysis those reporting low quality of life were almost 6 times more likely to experience retrospective memory problems. People reporting intermediate benzodiazepine use (using 1-6 times a week) were 8 times more likely to experience retrospective memory problems. There were effects approaching significance for those who used benzodiazepines almost every day (OR 6.67, 95%CI 0.98-45.46, p=0.053*),* for daily alcohol use, and daily injecting. In the stepwise analysis, benzodiazepine use independently contributed to 5.9% of the variance in retrospective memory.

Table 2. *Univariate Logistic Regression Predicting Likelihood of* Accidents and Injuries

	Major Accidents (Requiring medical attention)					**Minor Injuries** (Not requiring medical attention)				
Predictor Variables **Comparison Groups**	No accident % *n=132*	Accident % *n=29*	OR (significance)	Bootstrapped significance	(95%CI)	No Minor Injury % *n=121*	Minor Injury % *n=40*	95% (significance)	Bootstrapped significance	(95%CI)
Demographic characteristics										
Age (<30)	*41.7*	*41.4*	*0.99 (0.977)*	*0.972*	*0.44-2.24*	*39.7*	*47.5*	*1.38 (0.385)*	*0.402*	*0.67-2.83*
Male	*60.6*	*58.6*	*0.92 (0.843)*	*0.847*	*0.41-2.09*	*58.7*	*65.0*	*1.31 (0.479)*	*0.500*	*0.62-2.75*
Education (≤Year 10)	*67.4*	*75.9*	*1.52 (0.376)*	*0.399*	*0.60-3.83*	*66.9*	*75.0*	*1.48 (0.341)*	*0.353*	*0.66-3.33*
Income (<$13,000)	*93.1*	*96.6*	*2.07 (0.500)*	*0.241*	*0.25-16.98*	*93.4*	*94.9*	*1.31 (0.74)*	*0.642*	*0.27-6.44*
Unemployed	*15.2*	*17.2*	*1.17 (0.779)*	*0.777*	*0.40-3.42*	*14.9*	*17.5*	*1.21 (0.692)*	*0.702*	*0.47-3.16*
Unpartnered	*43.9*	*44.8*	*1.04 (0.930)*	*0.922*	*0.46-2.33*	*39.7*	*57.5*	*2.06 (0.051)*	*0.062*	*1.00-4.25*
Health factors										
Physical health problems: SF8 PCS[a]	*6.9*	*17.9*	***2.95 (0.073)***	***0.001***	*0.91-9.60*	*6.7*	*15.0*	*2.45 (0.119)*	*0.120*	*0.79-7.55*
Mental health problems: SF8 MCS[b]	*41.2*	*42.9*	*1.07 (0.873)*	*0.897*	*0.47-2.44*	*39.5*	*47.5*	*1.39 (0.375)*	*0.368*	*0.67-2.85*
Psychological Distress: K-10[c]	*60.8*	*58.6*	*0.91 (0.829)*	*0.833*	*0.40-2.08*	*58.6*	*65.8*	*1.36 (0.434)*	*0.429*	*0.63-2.92*
Risky drinking: AUDIT[d]	*23.6*	*33.3*	*1.62 (0.294)*	*0.272*	*0.66-3.99*	*23.2*	*31.6*	*1.53 (0.308)*	*0.324*	*0.68-3.44*
Quality of Life: PWI[e]	*28.8*	*37.9*	*1.51 (0.335)*	*0.334*	*0.65-3.5*	*24.8*	*47.5*	***2.74 (0.008)***	***0.008***	*1.30-5.78*
Drug use over past 6 months										
Daily alcohol	*7.6*	*13.8*	*1.95 (0.289)*	*0.254*	*0.57-6.72*	*6.6*	*15.0*	*2.49 (0.112)*	*0.104*	*0.81-7.68*
Daily cannabis use	*45.5*	*65.5*	***2.28 (0.054)***	***0.056***	*0.99-5.28*	*44.6*	*62.5*	*2.07 (0.052)*	*0.067*	*0.99-4.31*
Daily benzodiazepine use	*23.5*	*41.4*	*2.30 (0.052)*	*0.060*	*0.99-5.36*	*26.4*	*27.5*	*1.055 (0.896)*	*0.895*	*0.47-2.36*
Benzodiazepine use			*(0.079)*					*(0.787)*		
- *Low (Used 0-23 times)*	*53.0*	*34.5*				*51.2*	*45.0*			
- *Moderate (Used 24-143 times)*	*22.7*	*20.7*	*1.40 (0.548)*	*0.566*	*0.47-4.20*	*21.5*	*25.0*	*1.33 (0.540)*	*0.549*	*0.54-3.25*
- *Regular (Used 144-180 times)*	*24.2*	*44.8*	***2.85 (0.027)***	***0.021***	*1.13-7.17*	*27.3*	*30.0*	*1.25 (0.601)*	*0.614*	*0.54-2.91*
Daily opioid use	*58.3*	*44.8*	*0.58 (0.188)*	*0.183*	*0.26-1.30*	*54.5*	*60.0*	*1.25 (0.547)*	*0.541*	*0.61-2.59*
Daily tobacco use	*92.4*	*93.1*	*1.11 (0.900)*	*0.761*	*0.23-5.34*	*92.6*	*92.5*	*0.99 (0.990)*	*0.940*	*0.26-3.86*
Weekly amphetamine Use	*36.4*	*34.5*	*0.92 (0.849)*	*0.829*	*0.40-2.14*	*33.9*	*42.5*	*1.44 (0.326)*	*0.349*	*0.69-3.00*
Daily injection	*33.6*	*44.8*	*1.61 (0.255)*	*0.265*	*0.71-3.64*	*32.5*	*45.0*	*1.70 (0.155)*	*0.148*	*0.82-3.53*

*Table Interpretation: The predictor variables listed are the comparison group. The percentages reported are the percentages of the comparison group that either did or did not experience an event. Regarding the odds ratio (OR), an OR>1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. For example, as reported above, of those who *had not* experienced a major accident in the last 12 months, 6.9% had 'physical health problems', for those who *had* experienced an accident, 17.9% had 'physical health problems'. Those who had 'physical health problems' were 2.95 times more like to experience an accident than those who did not. For the benzodiazepine chronicity variable, the 'low use' category was the baseline group. [a]SF-8 Physical Component Score, [b]SF-8 Mental Component Score, [c]Kessler-10, [d]Alcohol Use Disorders Identification Test-C, [e]Personal Wellbeing Index

Table 3. Univariate Logistic Regression Predicting Likelihood of Cognitive Failures

	Prospective Memory (PM) Problem (Remembering to remember – e.g. an appointment, medication)					**Retrospective Memory (RM) Problem** (Remembering what you want to remember, e.g. information)				
Predictor Variables **Comparison Groups**	No PM problem % *n=123*	PM Problem % *n=35*	OR (significance)	Bootstrapped significance	95%CI	No RM Problem % *n=141*	RM Problem % *n=14*	OR (significance)	Bootstrapped significance	95%CI
Demographic characteristics										
Age (<30)	*39.8*	*45.7*	*1.27 (0.534)*	*0.547*	*0.60-2.71*	*41.1*	*41.2*	*1.00 (0.997)*	*0.998*	*0.36-2.79*
Male	*65.0*	*40.0*	***0.36 (0.009)***	***0.008***	*0.17-0.78*	*62.4*	*35.3*	***0.33 (0.038)***	***0.033***	*0.12-0.94*
Education (≤Year 10)	*69.1*	*74.3*	*1.29 (0.555)*	*0.540*	*0.55-3.02*	*68.8*	*82.4*	*2.12 (0.257)*	*0.183*	*0.58-7.74*
Income (<$13,000)	*93.4*	*97.1*	*2.39 (0.420)*	*0.211*	*0.29-19.76*	*93.6*	*100.0*	*- (0.999)*	*0.001*	*-*
Unemployed	*17.9*	*5.7*	*0.28 (0.095)*	*0.056*	*0.06-1.25*	*15.6*	*11.8*	*0.72 (0.678)*	*0.559*	*0.15-3.38*
Unpartnered	*48.0*	*28.6*	***0.43 (0.044)***	***0.034***	*0.19-.98*	*44.7*	*35.3*	*0.68 (0.463)*	*0.470*	*0.24-1.93*
Health factors										
Physical health problems: SF8 PCS[a]	*5.0*	*22.9*	***5.68 (0.003)***	***0.001***	*1.82-17.73*	*7.2*	*23.5*	***3.97 (0.037)***	***0.019***	*1.09-14.45*
Mental health problems: SF8 MCS[b]	*38.8*	*51.4*	*1.67 (0.186)*	*0.195*	*0.78-3.55*	*37.4*	*76.5*	***5.43 (0.005)***	***0.004***	*1.68-17.56*
Psychological Distress: K-10[c]	*55.6*	*82.4*	***3.73 (0.007)***	***0.003***	*1.44-9.69*	*57.8*	*93.8*	***10.96 (0.022)***	***0.020***	*1.41-85.39*
Risky drinking: AUDIT[d]	*24.3*	*29.4*	*1.30 (0.552)*	*0.559*	*0.55-3.03*	*23.5*	*41.2*	*2.28 (0.123)*	*0.113*	*0.80-6.49*
Quality of Life: PWI[e]	*26.8*	*45.7*	***2.30 (0.036)***	***0.030***	*1.06-4.99*	*27.0*	*64.7*	***4.97 (0.003)***	***0.001***	*1.72-14.37*
Drug use over past 6 months										
Daily alcohol	*5.7*	*17.1*	***3.43 (0.038)***	***0.022***	*1.07-10.98*	*6.4*	*23.5*	***4.51 (0.024)***	***0.007***	*1.22-16.70*
Daily cannabis use	*44.7*	*71.4*	***3.09 (0.007)***	***0.006***	*1.37-6.98*	*48.9*	*64.7*	*1.91 (0.225)*	*0.241*	*0.67-5.46*
Daily benzodiazepine use	*23.6*	*40.0*	*2.16 (0.057)*	*0.067*	*0.98-4.78*	*24.1*	*52.9*	***3.54 (0.016)***	***0.007***	*1.27-9.89*
Benzodiazepine use			*(0.076)*					***(0.031)***		
- *Low (Used 0-23 times)*	*53.7*	*34.3*				*53.2*	*17.6*			
- *Moderate (Used 24-143 times)*	*22.0*	*22.9*	*1.63 (0.339)*	*0.329*	*0.60-4.43*	*21.3*	*29.4*	***4.17 (0.061)***	***0.022***	*0.94-18.54*
- *Regular (Used 144-180 times)*	*24.4*	*42.9*	***2.75 (0.023)***	***0.018***	*1.15-6.59*	*25.5*	*52.9*	***6.25 (0.009)***	***0.004***	*1.60-24.49*
Daily opioid use	*55.3*	*60.0*	*1.21 (0.62)*	*0.651*	*0.57-2.61*	*56.0*	*58.8*	*1.12 (0.826)*	*0.826*	*0.40-3.11*
Daily tobacco use	*91.1*	*97.1*	*3.34 (0.257)*	*0.130*	*0.42-26.80*	*92.2*	*94.1*	*1.35 (0.779)*	*0.418*	*0.16-11.19*
Weekly amphetamine Use	*34.1*	*51.4*	*2.04 (0.066)*	*0.068*	*0.96-4.37*	*36.2*	*52.9*	*1.99 (0.184)*	*0.185*	*0.72-5.46*
Daily injection	*30.3*	*54.3*	***2.73 (0.011)***	***0.008***	*1.26-5.89*	*32.1*	*64.7*	***3.87 (0.012)***	***0.010***	*1.35-11.13*

*Table Interpretation: The predictor variables listed are the comparison group. The percentages reported are the percentages of the comparison group that either did or did not experience an event. Regarding the odds ratio (OR), an OR>1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. For example, as reported above, of those who *had not* experienced a prospective memory problem in the last 12 months, 30.3% injected daily, for those who *had* experienced an accident, 54.3% had injected daily. Those who injected daily were 2.73 times more like to experience a prospective memory problem than those who did not. For the benzodiazepine chronicity variable, the 'low use' category was the baseline group [a]SF-8 Physical Component Score, [b]SF-8 Mental Component Score, [c]Kessler-10, [d]Alcohol Use Disorders Identification Test-C, [e]Personal Wellbeing Index.

Table 4. Multivariate Logistic Regression Predicting Likelihood of Accidents and Injuries

	Major Accidents (Requiring medical attention)				**Minor Injuries** (Not requiring medical attention)			
	No Accident %	Accident %	OR (significance)	95%CI	No Minor Injury %	Minor Injury %	OR (significance)	95%CI
Predictor Variables **Comparison Groups**	*n=131*	*n=29*			*n=130*	*n=40*		
Age (<30)	*41.7*	*41.4*	*0.79 (0.639)*	*0.30-2.11*	*39.7*	*47.5*	*1.20 (0.680)*	*0.51-2.84*
Male	*60.6*	*58.6*	*1.22 (0.716)*	*0.42-3.49*	*58.7*	*65.0*	*1.17 (0.746)*	*0.46-2.98*
Education (≤Year 10)	*67.4*	*75.9*	*1.59 (0.402)*	*0.54-4.66*	*66.9*	*75.0*	*1.46 (0.442)*	*0.55-3.88*
Unemployed	*15.2*	*17.2*	*1.00 (0.996)*	*0.24-4.13*	*14.9*	*17.5*	*2.08 (0.227)*	*0.63-6.82*
Unpartnered	*43.9*	*44.8*	*1.10 (0.847)*	*0.41-2.97*	*39.7*	*57.5*	*2.04 0.111)*	*0.85-4.92*
Physical health problems: SF8 PCS[a]	*6.9*	*17.9*	*2.97 (0.141)*	*0.70-12.59*	*6.7*	*15.0*	*2.25 (0.246)*	*0.57-8.83*
Psychological Distress: K-10[b]	*60.8*	*58.6*	*0.62 (0.382)*	*0.21-1.82*	*58.6*	*65.8*	*1.20 (0.725)*	*0.44-3.22*
Quality of Life: PWI[c]	*28.8*	*37.9*	*1.13 (0.826)*	*0.38-3.33*	*24.8*	*47.5*	*1.89 (0.169)*	*0.76-4.68*
Daily alcohol	*7.6*	*13.8*	*1.59 (0.557)*	*0.34-7.46*	*6.6*	*15.0*	*1.90 (0.364)*	*0.48-7.58*
Daily cannabis use	*45.5*	*65.5*	*2.00 (0.157)*	*0.77-5.22*	*44.6*	*62.5*	*2.27 (0.058)*	*0.97-5.30*
Benzodiazepine use			*(0.072)*				*(0.663)*	
- *Low (Used 0-23 times)*	*53.0*	*34.5*			*51.2*	*45.0*		
- *Moderate (Used 24-143 times)*	*22.7*	*20.7*	*2.44 (0.168)*	*0.69-8.71*	*21.5*	*25.0*	*1.47 (0.478)*	*0.51-4.24*
- *Regular (Used 144-180 times)*	*24.2*	*44.8*	***3.88 (0.023)***	*1.20-12.50*	*27.3*	*30.0*	*0.87 (0.803)*	*0.30-2.56*
Daily opioid use	*58.3*	*44.8*	***0.29 (0.020)***	*0.10-0.82*	*54.5*	*60.0*	*1.19 (0.712)*	*0.48-2.92*
Daily tobacco use	*92.4*	*93.1*	*0.53 (0.483)*	*0.09-3.13*	*92.6*	*92.5*	*0.96 (0.964)*	*0.16-5.68*
Weekly amphetamine Use	*36.4*	*34.5*	*0.78 (0.632)*	*0.28-2.15*	*33.9*	*42.5*	*1.31 (0.547)*	*0.55-3.14*
Daily injection	*33.6*	*44.8*	*2.60 (0.069)*	*0.93-7.29*	*32.5*	*45.0*	*1.59 (0.312)*	*0.65-3.89*

*Table Interpretation: The predictor variables listed are the comparison group. The percentages reported are the percentages of the comparison group that either did or did not experience an event. Regarding the odds ratio (OR), an OR>1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. For example, as reported above, of those who *had not* experienced a major accident in the last 12 months, 58.3% used opioids daily, for those who *had* experienced an accident, 44.8% had used opioids daily. Those who used opioids daily were only one-third as likely to experience an accident as those who did not. For the benzodiazepine chronicity variable, the 'low use' category was the baseline group. [a]SF-8 Physical Component Score, [b]Kessler-10, [c]Personal Wellbeing Index.

Table 5. Multivariate Logistic Regression Predicting Likelihood of Cognitive Failures

	Prospective memory problem (Remembering to remember – e.g. an appointment, medication)				**Retrospective memory problem** (Remembering what you want to remember – e.g. information)			
	No PM problem % *n=122*	PM Problem % *n=35*	OR (significance)	95%CI	No RM Problem % *n=140*	RM Problem % *n=17*	OR (significance)	95%CI
Age (<30)	*39.8*	*45.7*	*1.65 (0.381)*	*0.54-5.06*	*41.1*	*41.2*		*0.08-2.31*
Male	*65.0*	*40.0*	*0.45 (0.181)*	*0.15-1.43*	*62.4*	*35.3*		*0.11-2.81*
Education (≤Year 10)	*69.1*	*74.3*	*0.68 (0.514)*	*0.21-2.18*	*68.8*	*82.4*		*0.32-12.38*
Unemployed	*17.9*	*5.7*	***0.03 (0.007)***	*0.00-3.80*	*15.6*	*11.8*	*0.41 (0.538)*	*0.03-6.88*
Unpartnered	*48.0*	*28.6*	***0.11 (0.002)***	*0.03-0.44*	*44.7*	*35.3*	*0.26 (0.119)*	*0.05-1.41*
Physical health problems: SF8 PCS[a]	*5.0*	*22.9*	***24.67 (0.001)***	*4.05-150.07*	*7.2*	*23.5*	*4.79 (0.161)*	*0.54-42.79*
Psychological Distress: K-10[b]	*55.6*	*82.4*	*2.64 (0.154)*	*0.70-9.98*	*57.8*	*93.8*	*3.59 (0.299)*	*0.32-39.93*
Quality of Life: PWI[c]	*26.8*	*45.7*	*2.34 (0.177)*	*0.68-8.03*	*27.0*	*64.7*	***5.84 (0.031)***	*1.17-29.15*
Daily alcohol	*5.7*	*17.1*	*3.83 (0.147)*	*0.62-23.63*	*6.4*	*23.5*	*9.32 (0.072)*	*0.82-106.40*
Daily cannabis use	*44.7*	*71.4*	***7.33 (0.002)***	*2.06-26.07*	*48.9*	*64.7*	*1.45 (0.632)*	*0.32-6.56*
Benzodiazepine use			*(0.733)*				*(0.094)*	
- *Low (Used 0-23 times)*	*53.7*	*34.3*			*53.2*	*17.6*		
- *Moderate (Used 24-143 times)*	*22.0*	*22.9*	*1.72 (0.486)*	*0.38-7.87*	*21.3*	*29.4*	***8.21 (0.047)***	*1.03-65.41*
- *Regular (Used 144-180 times)*	*24.4*	*42.9*	*1.58 (0.494)*	*0.42-5.90*	*25.5*	*52.9*	*6.67 (0.053)*	*0.98-45.46*
Daily opioid use	*55.3*	*60.0*	*0.87 (0.811)*	*0.27-2.83*	*56.0*	*58.8*		*0.05-1.81*
Daily tobacco use	*91.1*	*97.1*	*1.53 (0.750)*	*0.11-21.37*	*92.2*	*94.1*	*0.21 (0.306)*	*0.01-4.17*
Weekly amphetamine Use	*34.1*	*51.4*	***3.71 (0.035)***	*1.10-12.51*	*36.2*	*52.9*	*1.62 (0.546)*	*0.34-7.67*
Daily injection	*30.3*	*54.3*	*2.43 (0.113)*	*0.81-7.26*	*32.1*	*64.7*	*4.52 (0.070)*	*0.88-23.11*

*Table Interpretation: The predictor variables listed are the comparison group. The percentages reported are the percentages of the comparison group that either did or did not experience an event. Regarding the odds ratio (OR), an OR>1 means that the event (e.g. accident) was more likely in the comparison group, an OR<1 means it was more likely in the baseline group. For example, as reported above, of those who *had not* experienced a prospective memory problem in the last 12 months, 44.7% used cannabis daily, for those who *had* experienced an accident, 71.4% used cannabis daily. Those who used cannabis daily were 7.33 times more like to experience a prospective memory problem than those who did not. For the benzodiazepine chronicity variable, the 'low use' category was the baseline group. [a]SF-8 Physical Component Score, [b]Kessler-10, [c]Personal Wellbeing Index.

Table 6. *Nagelkerke R2 values for Stepwise analysis, for each Outcome variable*

	Accidents	Injuries	Prospective Memory	Retrospective Memory
Model 1[a]	0.036	0.120	0.312	0.286
Model 2[b]	0.134	0.183	0.517	0.423
Model 3[c]	0.188	0.190	0.521	0.482

[a]Model 1 Included demographic predictors only (age, sex, education, employment, partnered, physical health problems, psychological distress, and quality of life), [b]Included variables from Model 1 plus drug use variables, excluding benzodiazepines (daily alcohol, daily cannabis, daily opioid, daily tobacco, weekly amphetamine, and daily injecting).[c]Included variables from Models 1 and 2 plus the graded benzodiazepine variable (low, moderate, and regular use).

DISCUSSION

This study aimed to investigate the characteristics of injecting drug use associated with decreased safety. Results showed a variety of predictors were associated with the outcome measures, which is consistent with the premise that there are a range of risk factors impacting on the lives of injecting drug users. Even with the multitude of other hazardous factors and behaviours, moderate benzodiazepine use independently contributed to an increased risk of retrospective memory problems (OR 8.21, 95%CI 1.03-65.41, *p*=0.047), and regular benzodiazepine use was associated with major accidents (OR 3.88, 95%CI 1.20-12.50, *p*=0.023).

It is commonly recommended that the prescription of benzodiazepines is best avoided in people who misuse other drugs. This is due to the high risk of adverse events that can occur when benzodiazepines are used in combination with other central nervous system depressants (such as alcohol or opioids), including sedation, respiratory depression, and death (Royal Australian College of General Practitioners, 2015). Benzodiazepine use is associated with an increase in general harms linked with injecting drug use, including poorer physical and mental health (Darke, Hall, Ross, & Wodak, 1992; Darke et al., 2010). There is also evidence that people participating in opioid substitution therapy, who regularly or occasionally use

benzodiazepines, have more adverse outcomes (Mental Health and Drug and Alcohol Office (MHDAO), 2006). It is not recommended that prescribers provide substitution benzodiazepine therapy for those who are using benzodiazepines illicitly (Royal Australian College of General Practitioners, 2015). Despite these recommendations, many of this sample are regular benzodiazepine users. That benzodiazepine use is so common in a population at high risk of negative outcomes, does emphasise the importance of greater control of benzodiazepine prescription.

In this sample of people who inject drugs, reported rates of accidents, injuries, and prospective and retrospective memory problems occurred in significantly higher proportions compared to the general population. Comparable research in the UK (Wadsworth et al., 2005) found that in a random postal population study (*n*=7979), 11% of respondents reported an accident (excluding traffic accidents), comparatively 18% of this sample had reported at least one accident ($\chi^2(1_{n=}8139)=7.34$, $p=0.006$). Likewise when comparing minor injury rates, 14% of the UK general population sample experienced quite or very frequent injuries, compared to 25% of this injecting drug sample ($\chi^2(1_{n=}8140)=14.35$, $p<0.001$). General population data were obtained for the PRMQ from a large sample (*n*=551) by Crawford and colleagues (2003). Assuming a standard distribution, prospective and retrospective memory problems are expected to occur in the general population at a rate of less than 2.3%. Rates in the PWID sample occurred at significantly higher levels for both prospective memory, with 22% experiencing problems ($\chi^2(1_{n=}709)=73.21$, $p<0.001$), and retrospective memory with 11% reporting problems ($\chi^2(1_{n=}709)=20.80$, $p<0.001$). Elevated rates of incidents are indicative of the hazardous lifestyle led by this group; the variables examined here go some way towards understanding this risk.

Current findings indicate that this cohort experiences low levels of health and well-being. For example, 30% of this injecting drug population reported a personal wellbeing index (PWI) score of more than two standard deviations below the mean (<49.73), indicating very low quality of life. Comparatively, in a general population survey of 34,804 people, only 4.4% fell below a score of 50 (Cummins et al., 2011).

This difference in proportions is statistically significant ($\chi^2(1_n=34,973)=241.20$, $p<0.001$). Extensive research on the PWI suggests that a normal level of wellbeing, usually around 75 points, allows people to feel good about themselves, be motivated to conduct their lives, and optimistic (Cummins et al., 2011). It is suggested that most people are able to maintain their quality of life around this normal range, despite a variety of difficult life events. When levels do fall below this range, people are at risk of depression and low wellbeing. Inability to maintain homeostasis of wellbeing is influenced by genetic and environmental factors, but can also be strengthened by certain aspects, like personal relationships. Likewise, when examining psychological distress, 60% of the current group were classified in the 'very high' level of distress, which is significantly elevated ($\chi^2(1_n=20,661)=384.37$, $p<0.001$) compared to a national rate of 10.8%, calculated from 20,500 people in the National Health Survey (Australian Bureau of Statistics, 2012. Rating within this very high level of distress places individuals at a high risk of depression. That such a considerable proportion of this PWID cohort, are so markedly below the average range on these measures, is indicative of the high levels of stressful life events experienced, combined with a lack of protective factors, and is likely to have a substantial impact on their continued health and wellbeing.

Much of the previous accident research has relied on data gained from presentation to medical services. A strength of the current study is that it follows the research of Wadsworth and colleagues (for example: Wadsworth, Moss, et al., 2003; Wadsworth et al., 2005) in examining safety incidents of a lower severity. Given that deficits in cognitive processes have been shown to predict propensity for accident involvement (Wallace & Vodanovich, 2003), it is extremely important that these lower level incidents continue to be involved in study designs. However with this comes a reliance on self-report data. Whilst the use of self-report is well-established in this population (Darke, 1998), it is necessary to find a time frame that allows for accurate recall, whilst providing sufficient time for exposure to accidents and injuries. Research suggests that an extended period of recall leads to

underestimation of minor injuries; however, reports of more significant injury are not affected within a 12 month period (Harel et al., 1994; Moshiro, Heuch, Astrom, Setel, & Kvale, 2005). Considering the 6-month time frame used in this study, and the fact that reported incident rates far exceed general population rates, it appears that incident recall has not been significantly affected in this study; a viable concern given the possibly cognitively compromised population studied.

It is notable that even in the context of high severity injecting drug use, substances that may be considered a low treatment priority, such as alcohol and cannabis, have significant associations with safety. From a research consideration, this demonstrates the importance of screening and controlling for and including these substances in analyses. Regarding clinical practice, it shows the importance of harm minimising interventions that target all regular drug use, not just the substance that is deemed the most hazardous, or is the presenting issue.

This research found that benzodiazepines independently contribute to an increased risk of incidents in a PWID cohort; a group for whom safety and well-being is already compromised. It is often argued that benzodiazepine users are most at risk during initial onset of use and side-effects decrease with time. However, with 28% of the cohort using at least daily for 6 months, they are clearly chronic users, and they still appear to be negatively affected by the use of benzodiazepines. From a clinical practice consideration, these findings support the importance of further regulating benzodiazepine prescription, and increasing treatment options for those living with drug and alcohol addictions.

As expected, there are a range of predictors that influence the safety of people who inject drugs, including some that are commonly seen as more benign such as alcohol, cannabis, and prescribed benzodiazepines. The use of benzodiazepines in people who inject drugs is countraindicated. The findings of the current study show that there are additional and independent detrimental effects of benzodiazepines on safety in this cohort. More effective management of benzodiazepine use is an

important component of improving the remarkably low levels of self-rated well-being, and high psychological distress found in this cohort.

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8 The Subjective Experience of Chronic Benzodiazepine Consumers

CHAPTER 8: THE SUBJECTIVE EXPERIENCES OF CHRONIC BENZODIAZEPINE CONSUMERS

Preface

Study 1 and *Study 2* examined the association between benzodiazepine use, other confounding variables, and experience of safety incidents. Reports of safety incidents were elevated in both the general population sample (*Study 1)* and a sample of people who inject drugs (*Study 2).* Comparatively, the focus of this chapter is to report on the subjective perceptions of a group of chronic benzodiazepine users (*Study 3).* Data for *Study 1 and 3* were collected through the same online survey. Respondents were asked about their awareness and experience of side-effects (*Research Question 4*), perceived impairment to driving ability (*Research Question 5),* and general worries and concerns related to benzodiazepine use (*Research Question 6).* This chapter helps to inform the findings from *Study 1* and *Study 2,* by providing details about the consumer's experience.

ABSTRACT

Objective

Benzodiazepines have been well-studied for many years; however, surprisingly few studies investigate the subjective experiences of regular benzodiazepine consumers. There is evidence that benzodiazepine use is often chronic, and that psychomotor impairment persists in these users. Therefore alongside this objective evidence, it is important to understand how chronic consumers understand, perceive, and monitor, their use of benzodiazepines.

Method

Data was collected from 129 participants using an online survey that ran from 2013-2015. Participants were required to; be over 18 years of age, be an Australian resident, have used a benzodiazepine during the last 12 months, and have a current driver's license. A range of demographic, and benzodiazepine use information was gathered, as well as information about subjective perceptions of benzodiazepine use.

Results

Duration, dose, and frequency of benzodiazepine use were in excess of standard clinical recommendations for the majority of this sample. Symptoms of dependence, in particular withdrawal symptoms, were reported as a barrier to reduction of benzodiazepine use. Overall, the respondents had poor knowledge of benzodiazepine side-effects, and reported that the education that they had received about benzodiazepines was minimal. Side-effects were regularly experienced by the group, and did not abate, particularly for the most chronic users.

Conclusion

The attitudes of benzodiazepine users in this sample were mixed. For a small proportion, benzodiazepines were seen as positive, and no problems were had with dependence or escalation of use. Unfortunately for many, benzodiazepines were reported to no longer be effective, and were associated with negative effects and symptoms of dependence. A benzodiazepine contract, similar to that used in opioid treatment, is suggested as a strategy to manage ongoing high rates of benzodiazepine prescription.

INTRODUCTION

Benzodiazepines are a highly effective psychoactive drug class, used to treat a variety of conditions including anxiety, sleep disorders, and epilepsy (Barker, Jackson, Greenwood, & Crowe, 2003). Concerns regarding negative side-effects and dependence, has led to more restrictive prescribing of benzodiazepines. However, current research suggests benzodiazepines remain widely prescribed worldwide (Islam, Conigrave, Day, Nguyen, & Haber, 2013). Experimental studies examining benzodiazepine use are extensive, but there has been a comparative absence of research examining the experiences and perceptions of regular benzodiazepine consumers (Barker, Greenwood, Jackson, & Crowe, 2004).

Current clinical guidelines recommend that benzodiazepines should be avoided if possible, or if necessary used *at the lowest possible dose* and *for the shortest time period* feasible (National Health and Medical Research Council, 1991; Royal Australian College of General Practitioners, 2000). These guidelines have been established based on; the known rapid development of tolerance and subsequent reduced efficacy to the desired effects (Vinkers & Olivier, 2012), established cognitive and psychomotor deficits (Barker et al., 2003), and the growing body of evidence suggesting long-term harm associated with use, such as an increased risk of dementia (Billioti deGage et al., 2012). Alongside these recommendations, more restrictive practices have been established. For example, alprazolam has recently been rescheduled in Australia to a restricted S8 medication, which is the same level of restrictions as are required for strong opioids such as morphine and oxycodone (The Royal Australian College of General Practitioners, 2013).

Whilst the guidelines directing prescription that have been released over the past 35 years are evidence based and well-intentioned, there are no doubt, some unintended consequences of these directives, for those that are prescribed benzodiazepines. Understanding the consumer's experience is essential for clinicians, and can help to guide interventions. For example, knowing the typical positive and negative factors that lead to consumers continuing benzodiazepine

use, could help to guide motivational interviewing techniques. Similarly, knowing the withdrawal symptoms that consumers usually find most difficult to manage, may pre-empt a conversation around techniques to manage these symptoms. Information about the subjective experiences of benzodiazepine users, will only help to enrich data gained from quantitative studies.

The acute effects of benzodiazepine use are well-known, with new users commonly cautioned about drowsiness, memory loss, confusion, and psychomotor impairment (Barker et al., 2003). It is becoming increasingly accepted that many of these side-effects continue even with long-term use (Barker et al., 2004). Particularly, research has focused on the impact of benzodiazepine use on driving, although much of the experimental research examines naïve benzodiazepine users; see Kelly, Darke, and Ross (2004) for a review of drugged driving research. As an error prone and potentially fatal activity, the interest in driving is not surprising; however, few studies examine the driving skills of benzodiazepine users from a subjective point of view. There is some evidence that benzodiazepine use impairs metacognition, one aspect of which is the ability to accurately judge one's performance, and detect impairment (Bacon et al., 1998; Mintzer & Griffiths, 2003; Roache, Cherek, Bennett, Schenkler, & Cowan, 1993). Given the potential discrepancy between impairment and perception of such impairment, the importance of the subjective experience of benzodiazepine users becomes clear. Particularly so, as medication labels advise self-monitoring of impairment, for example the Australian medication Label 12 states '*if affected do not drive a motor vehicle or operate machinery*' (Sansom, 2002).

Similarly, it is also essential to recognise the positive reasons for which people use benzodiazepines. Benzodiazepines remain a useful treatment option due to their effectiveness and speed of onset, relatively good ability to be tolerated, capacity to be used 'as needed', and comparative safety in overdose (Starcevic, 2012). Evidence suggests benzodiazepines remain efficacious for several conditions, for example; in the short-term treatment of certain anxiety disorders, in the period before other

medications, such as antidepressants become effective, or for managing acute alcohol withdrawal (Baldwin et al., 2013). Compliance with treatment guidelines by keeping dosage short-term and intermittent, is likely to reduce problematic usage. Whilst there is a vast amount of literature on the negative effects of benzodiazepines, there is comparatively little documented about those who are able to use without problems of dependence. As Baldwin and colleagues (Baldwin et al., 2013; pg 971) conclude "benzodiazepines have a range of beneficial effects and a range of untoward effects, like all forms of pharmacological and psychological treatment". Recognising this, and acknowledging the varying experiences of consumers is essential.

As has been demonstrated, there are many ways in which benzodiazepine prescription can be optimised, but the risk of dependence and negative consequences persists. What remains unclear is just how well this information is disseminated to patients. Within Australia, the process of prescribing benzodiazepines, is left largely to the judgement of the individual prescriber, providing they adhere to government regulations. The level of information provided will depend in part on the characteristics of the health professional, such as their own or organisational preferences, time available, and communication skills. Without doubt, patient variables will also influence the level of information retained. It is well established that patient's memory for information provided at the doctors is poor (Kessels, 2003). This is particularly the case when the patient is older or anxious, as is commonly the case with benzodiazepine users (Kessels, 2003). Consequently, also of interest in this study is whether benzodiazepine users retain information pertinent to their safety.

The main focus of this study is to conduct a qualitative exploration of the views of regular benzodiazepine users regarding safety and well-being. The aims of the study are as follows:

- To investigate awareness and experience of benzodiazepine side-effects, specifically:

  - What do regular consumers know about the side-effects of benzodiazepines?
  - From what sources is information about side-effects obtained?
  - What side-effects do consumers detect and does this change over time?

- To explore whether regular benzodiazepine consumers perceive any impairment to their driving ability:

  - Do benzodiazepine consumers detect any impairment to their driving ability when first using benzodiazepines?
  - Does any impairment change over time as benzodiazepine use progresses?
  - Do people take any precautions regarding benzodiazepine use and driving?

- To conduct an exploration of the perceptions and viewpoints of benzodiazepine consumers with varying patterns of usage, and with a particular focus on their worries and concerns.

This research will explore the perceptions of regular benzodiazepine users. The information gained in this study will assist professionals with understanding the experiences of benzodiazepine users, and in turn, inform clinical practice.

METHOD

Participants

Data was collected through an online survey run from 2013-2015. The survey was marketed to Australian residents through advertising in doctor's surgeries, pharmacies, hospitals, and targeted social media. On completion of the survey, participants could choose to enter a prize pool for 1 of 3 $500 vouchers. A total of 251 participants initiated the survey, with 122 participants excluded from the

analysis due to incomplete data (*n*=129). This high exclusion rate occurred because there were many participants who had entered no data at all (*n*=37), or only demographic information (*n*=57), before exiting the survey. Initial survey questions excluded those who were under 18 years of age, had not used a benzodiazepine in the last 12 months, or who did not agree to informed consent statements.

To clarify benzodiazepine use, participants were questioned on the duration and frequency of their use. This information was then used to guide a post-hoc development of three different categories of benzodiazepine chronicity. In the survey participants were asked to indicate which answer best reflected their pattern of benzodiazepine use: use daily for – less than a month, greater than a month, or greater than a year; or use occasionally for – less than a month, greater than a month, or greater than a year. At the point of analysis this self-identified pattern was verified with information from other survey questions, including; start and finish date of using benzodiazepines, total days using benzodiazepines, and number of days in last month using benzodiazepines. In order to have sufficient numbers in each chronicity group, a pragmatic decision was made to combine some of these self-identified patterns of use into three main patterns of chronicity. The three chronicity groups developed were as follows; short-term users (those who had been using *daily* or *occasionally* for *less than one year*), intermittent users (those who had used *occasionally*, for a period *greater than one year*) and chronic users (those who had used *daily* for a period *greater than one year*). The development of the chronicity groups was guided by the following considerations; (1) allocating sufficient participant numbers to each group, (2) promoting homogeneity within each group and (3) allowing comparisons to be made across key elements of interest, namely the different effects of *duration* and *frequency* of use.

Procedure

The survey took approximately 30 minutes to complete, and non-relevant sections were excluded based on initial screening questions, reducing the total time

required. Major survey sections included questions on: demographic information, benzodiazepine use, licence and driving, road accidents, perceptions of benzodiazepines, general accidents, memory, alcohol and other drug use, health, and other medication use (antidepressants, antipsychotics, painkillers, and other psychotropic medications). Ethical approval was granted by the Tasmanian Social Sciences Human Research Ethics Committee (approval number H0012343 - Benzodiazepines; Use, health and driving).

Measures

Side-Effects

Survey questions focused on three aspects of side-effects; knowledge of side-effects, sources of information, and side-effects experienced. As a test of user knowledge, respondents were asked to identify commonly occurring benzodiazepine side-effects. The question used in the survey was: *Tick all of the symptoms listed below that you think could be a side-effect of taking benzodiazepines.* There were a total of 10 answers to choose from, including seven commonly occurring benzodiazepine side-effects (*drowsiness, sedation, light-headedness, double vision, slurred speech, memory loss, and ataxia - difficulty with coordination*). These symptoms were included as they were identified as the most commonly occurring side-effects in the Australian Medicines Handbook (Australian Medicines Handbook, 2015). Also included were three side-effects not usually associated with benzodiazepine use (*nausea, indigestion, constipation)*, which were included to verify discrimination and accuracy of participant's answers.

To investigate the sources of information from which benzodiazepine users received information about side effects, the survey used the following question: *When you first started using Benzodiazepines how did you learn about the possible negative side effects?* There were eight answer options provided, and respondents could select all that applied (*I was not aware of the side-effects, the Doctor told me, the Pharmacist told me, I read the information in the box, I saw a warning label on the*

box, a friend/family member told me, the internet, and 'other'). These answer options were chosen as they represent best practice (e.g. being told by doctor, and/or pharmacist), Australian legal requirements (e.g. warning labels and information in box), or common non-professional sources of information for consumers (e.g. family/friend and the internet).

As an indication of side-effects encountered and change over time, respondents were asked about their experience on six key symptoms. Respondents were asked to indicate whether they had experienced a symptom, for example: *Have you experienced any confusion that you feel is related to your benzodiazepine use?* Respondents who answered 'yes' were further questioned about how this symptom had changed over time, for example: *Since you began taking benzodiazepines has this confusion; stayed the same, worsened, improved.* Side-effects investigated in this question, were the same as those used in the initial test of consumer knowledge. The exception to this was 'sedation' and 'drowsiness', which were combined into one category 'daytime drowsiness', in order to avoid those using benzodiazepines for night-time sedation reporting this as a side-effect.

Driving Safety

To examine the self-detected effects on driving, consumers were asked about the impact they felt benzodiazepines had on their driving ability, when they first started taking benzodiazepines (survey question: *When you first started taking benzodiazepines [e.g. for the first month], how did you think they impacted on your driving ability?*), and then at the current time (survey question: *How do you think your use of benzodiazepines currently impacts on your driving ability?*). Respondents were then asked to indicate any safety precautions they used (survey question: *Whilst taking benzodiazepines have you taken any safety precautions in regards to driving?*) Seven precautions were provided as answer options; *I did not take any precautions, I stopped taking benzodiazepines, I did not drive at all, I did not drive immediately after I had taken a benzodiazepine, I drove more slowly, I took other things to counter any side-effects and 'other'.*

General perceptions and concerns

To gain insight into the general concerns of regular benzodiazepine users, an open-ended question was used to gather this information. Respondents were first asked about whether they worried about using benzodiazepines (survey question: *Do you worry about using Benzodiazepines? Yes or No*), and were then invited to elaborate on this answer if they wished. An open-ended question was also included at the end of the survey: *We're really interested in the positive and negative effects that benzodiazepines have on people's lives. The questionnaire can't capture all of this, so if there are any other comments you would like to make, please let us know in the space below.* This question was initially included to improve consumer satisfaction, but due to the quantity of information it revealed related to benzodiazepine use, answers to this question were merged with the data from the other open ended question. Information gained from these questions was organised into key themes. Statements from respondents reported in the results section are identified by the user group they were allocated to (*St*=short-term users, *Int*=intermittent Users, *Ch*=Chronic Users), and numbered according to the order in which the participant completed the survey.

Related Variables

The Short-Form Health Surveys are a group scales providing a general measure of self-rated health. Whilst the SF-36 has been extensively tested and used within Australia, a briefer form, the SF-12 version 1 (Ware, Kosinski, & Keller, 1995) was chosen for brevity, and was re-scaled to fit SF-36 norms. The SF-12 measures eight domains, across the last 4 weeks; physical functioning, role functioning related to physical problems, bodily pain, general health, vitality, social functioning, role functioning related to emotional problems and mental health. These domains then combine to form a physical component summary (PCS) score and mental component summary (MCS) score. For each scale, scores range between 0-100, with higher scores equating to better health. Norms from a South Australian population study were chosen as the most up-to-date and representative Australian

norms (Avery, Dal Grande, & Taylor, 2004). Those scoring less than 2SD below the mean were identified as the at risk group (physical component summary score ≤28.62 and mental component summary score ≤34.79).

The Kessler-10 is a 10-item questionnaire providing a global indication of anxiety and depression symptoms (Kessler & Mroczek, 1994). Symptoms experienced over the past 4 weeks are rated on a 5 point scale ranging from 'none of the time' to 'all of the time'. Whilst different cut-off scores are used within Australia, the convention set by the Australian Bureau of Statistics was followed, with total scores equal to or above 22, taken as an indication of high psychological distress (2003). Andrews and Slade (Andrews & Slade, 2001) found that the K-10 appropriately identified those classified by the Composite International Diagnostic Interview v2.0, as having any DSM-IV or ICD-10 anxiety or affective diagnosis (at a score of 22; sensitivity=0.55, specificity=0.95).

Alcohol use was assessed through the use of the AUDIT-C; a shortened version of the well-established AUDIT tool (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). The AUDIT-C is scored on a scale of 0-12, with each question scored between 0 and 4. Different cut-off scores are recommended for men (Bush et al., 1998) and women (Bradley et al., 2003), with hazardous drinking identified through a score of 3 or more in women (sensitivity=0.66, specificity=0.94) and 4 or more in men (sensitivity=0.48, specificity=0.99).

The Severity of Dependence Scale (Gossop et al., 1995) was used to screen for benzodiazepine dependence. The SDS is a short five-item scale that can be used to measure the degree of dependence on different types of drugs. Each SDS item is concerned with a psychological aspect of dependence. The diagnostic capability of the SDS in regards to benzodiazepines was established in a sample of 100 regular benzodiazepine users (de Las Cuevas, Sanz, De Las Fuente, Padilla, & Berenguer, 2000); a score above six was used as an indication of benzodiazepine dependence (sensitivity=97.9%, specificity=94.2%).

Data Analysis

Data about detection and change in side-effects, and driving related information was obtained through a series of closed-ended questions and summarised with descriptive statistics. Data from the open-ended questions was analysed using content analysis, which involves identifying and grouping themes and categories within data (Pope & Mays, 1995). Two multidisciplinary raters (Psychologist and Pharmacist) carefully and repeatedly studied the data from the open ended-questions, and identified emerging themes within text segments. Themes reported in the results are those that occurred repeatedly across the data. Themes were not chosen beforehand, so this reduced the chance of preconceptions influencing the findings. Attention has been given to deviant case analysis (Kitzinger, 1995). Given that the sample sizes in the study were smaller than expected, and thus the resultant power of analyses would be low, the decision was made to focus on descriptive analysis.

RESULTS

A total of 129 subjects participated in this study, and results were examined across three categories of benzodiazepine chronicity (table 1).As expected the groups differed on benzodiazepine use with the chronic group having a higher average dosage and frequency of benzodiazepine use compared to the other groups.

Table 1. *Analysis of Variance for Key Variables of interest Across Benzodiazepine Chronicity Categories*

	Short-term Use *(SD)*[a] *N=24*	Intermittent Use *(SD)* *N=55*	Chronic Use *(SD)* *N=50*	ANOVA	Significant comparisons[b]
Reason for Benzodiazepine Use					
Sleep only	*n*=9 (37.5%)	*n*=27 (49.1%)	*n*=23 *(46.0%)*	n/a	
Anxiety only	*n*=12 (50%)	*n*=20 (36.4%)	*n*=22 (44%)	n/a	
Other/multiple reasons	*n*=3 (12.5%)	*n*=8 (14.5%)	*n*=5 (10%)	n/a	
Benzodiazepine Use					
Mean Length of Use (days)[c]	168.8 *(243.8)*	2416.7 *(3840.8)*	3053.9 *(3605.1)*	*F*(2,126)=6.05, *p*=.003	ST<Int, *p*=.020; ST<Chr *p*=.002
Mean Total days used per month	14.9 *(17.7)*	10.3 *(13.9)*	38.1[d] *(45.6)*	*F*(2,115)=10.65, *p*<.001	ST<Chr, *p*=.013; Int<Chr, *p*<.001
Mean Total Dose per month[e]	229.5[f] *(381.9)*	231.6 *(432.1)*	919.3 *(1816.4)*	*F*(2,115)=4.81, *p*=.010	Int<Chr, *p*=.013
Other variables of interest					
Mean Age	30.9 *(11.9)*	39.1 *(14.7)*	40.5 *(11.7)*	*F*(2,126)=4.64, *p*=.011	ST<Int, *p*=.031; ST<Chr, *p*=.010
Mean AUDIT-C[g]; Average Score	4.1 *(3.6)*	4.2 *(3.2)*	3.5 *(3.5)*	*F*(2,102)=0.54, *p*=.587	-
Mean Kessler-10[h]	27.1 *(8.3)*	21.5 *(8.3)*	27.8 *(10.5)*	*F*(2,95)=5.35, *p*=.006	Int<Chr, *p*=.008
Mean SF-12 MCS[i]	33.0 *(11.9)*	40.5 *(13.1)*	35.6 *(14.0)*	*F*(2,99)=2.60, *p*=.079	-
Mean SF-12 PCS[j]	47.4 *(11.3)*	47.6 *(12.3)*	43.1 *(12.8)*	*F*(2,99)=1.54, *p*=.219	-
Mean GP visits (past year)	9.1 *(8.8)*[k]	6.7 *(5.2)*	12.4 *(8.4)*	*F*(2,107)=7.002, *p*=.001	Int<Chr, *p*=.001
Mean Average score BZD SDS[l]	4.2 *(4.1)*	2.6 *(3.3)*	7.3 *(4.4)*	*F*(2,114)=18.87, *p*<.001	ST<Chr, *p*=.008; Int<Chr, *p*=<.001

Benzodiazepine chronicity categories: Short-term Use (using benzodiazepines daily or occasionally for less than one year), Intermittent Use (using benzodiazepines occasionally for greater than one year), Chronic Use (using benzodiazepines daily for greater than one year). [a]*SD=Standard Deviation.* [b]Tukey's method used for post-hoc tests. ST=short-term group. Int=intermittent group. Chr=Chronic group. [c]Calculated using start and finish dates for each benzodiazepine, therefore does not represent the number of days on which benzodiazepines have been consumed, but rather the period of time that benzodiazepines have been used for. Additionally, this total is additive across each benzodiazepine type used. [d]This is a cumulative sum across all benzodiazepine types, therefore the mean of 38.13 for chronic users reflects the use of more than one benzodiazepine a day. [e]Converted to an equivalent diazepam dose in milligrams. [f]This monthly amount is equivalent to 7.63mg a day, which is less than the 10mg defined daily dose. [g]Kessler-10 (Kessler & Mroczek, 1994); total scores ≥22, were taken as an indication of high psychological distress. [h]Different cut-off scores are recommended for men (Bush et al., 1998) and women (Bradley et al., 2003), on the AUDIT-C with hazardous drinking identified through a score of 3 or more in women (sensitivity=0.66, specificity=0.94) and 4 or more in men (sensitivity=0.48, specificity=0.99). [i]Mental Component Score; scores range between 0-100, with higher scores equating to better health. [j]Physical Component Score: scores range between 0-100, with higher scores equating to better health [k]In this group there was a participant who identified as having 300 GP visits in the past year. This extreme outlier was removed as it severely inflated the result for this short-term user group, and was most likely an error during survey completion. [l]BZD=benzodiazepine, SDS=Severity of Dependence Scale. A score above 6 corresponds with benzodiazepine dependence, as determined by the Composite International Diagnostic Interview (specificity=94.2%, sensitivity=97.9%).

Knowledge and Experience of Side-Effects

Table 2 presents the results related to consumers' experience of side-effects. A brief test of user knowledge regarding benzodiazepines side-effects revealed that very few respondents were able to correctly identify side-effects, with only 3 respondents scoring all 10 answers correctly.

Also of interest were the sources of information regarding the potentially negative side-effects of benzodiazepines (Table 2). The most commonly reported source of information across the groups was the information pamphlet provided within the box. Surprisingly low numbers of respondents reported they had received information from their Doctor or Pharmacist, and even fewer stated that they had seen a warning label on the box. Answers provided in an 'other' section included: "*learning through own profession*", "*trial and error*", and "*I was not given sufficient information from my GP and I would have never taken Alprazolam if I had been*".

Respondents were asked to identify side-effects that they had experienced from a commonly occurring list of symptoms. Overall the short-term and chronic user groups were more likely to report the occurrence of negative symptoms compared to the intermittent users (Table 2). Figure 1 represents the experience of change in these symptoms over time. Unfortunately for a large proportion of the sample, symptoms seemed to stay the same or worsen, suggesting that tolerance likely does not universally develop over time, particularly in respect to cognitive deficits. Reports of memory loss were particularly of note, with most of the group reporting no resolution in this symptom; only 30% of the short-term users reported memory loss had improved over time.

Table 2. *Consumer reported Knowledge of Side-Effects, Sources of Information regarding Side-Effects, and Personal Experience of Side-Effects, across Benzodiazepine Chronicity*

	Short-term Users (*n*=24)	Intermittent Users (*n*=55)	Chronic Users (*n*=50)
Knowledge of Side-Effects Survey Question: *"Tick all of the symptoms listed below that you think could be a side-effect of taking benzodiazepines"*			
Scored 0-5 answers correct	31.3% (*n*=5)	43.9% (*n*=18)	53.8% (*n*=21)
Scored 6-9 answers correct	62.5% (*n*=10)	53.7% (*n*=22)	43.6% (*n*=17)
Scored all answers correct	6.3% (*n*=1)	2.4% (*n*=1)	2.6% (*n*=1)
Sources of information Survey Question: "*When you first started using benzodiazepines, how did you learn about the possible negative side effects?"*			
I was not aware of the side-effects	16.7% (*n*=4)	12.7% (*n*=7)	20.0% (*n*=10)
The Doctor told me	25.0% (*n*=6)	34.5% (*n*=19)	34.0% (*n*=17)
The Pharmacist told me	16.7% (*n*=4)	21.8% (*n*=12)	20.0% (*n*=10)
I read the information in the box	41.7 % (*n*=10)	34.5% (*n*=19)	36.0% (*n*=18)
I saw a warning label on the box	12.5% (*n*=3)	16.4% (*n*=9)	14.0% (*n*=7)
A friend/family member told me	12.5% (*n*=3)	1.8% (*n*=1)	4.0% (*n*=2)
The internet	29.2% (*n*=7)	29.1% (*n*=16)	26.0% (*n*=13)
Side-Effects experienced Survey Question: "*Have you ever experienced any [insert symptom] that you feel is related to your benzodiazepine use?"*			
Daytime drowsiness	57.9% (*n*=11)	40.8% (*n*=20)	59.1% (*n*=26)
Poor concentration	47.4% (*n*=9)	24.5% (*n*=12)	54.5% (*n*=24)
Light-headedness	44.4% (*n*=8)	18.8% (*n*=9)	28.6% (*n*=12)
Memory Loss	55.6% (*n*=10)	16.3% (*n*=8)	54.5% (*n*=24)
Slurred speech	44.4% (*n*=8)	15.2% (*n*=7)	38.1% (*n*=16)
Confusion	35.3% (*n*=6)	8.2% (*n*=4)	37.5% (*n*=15)

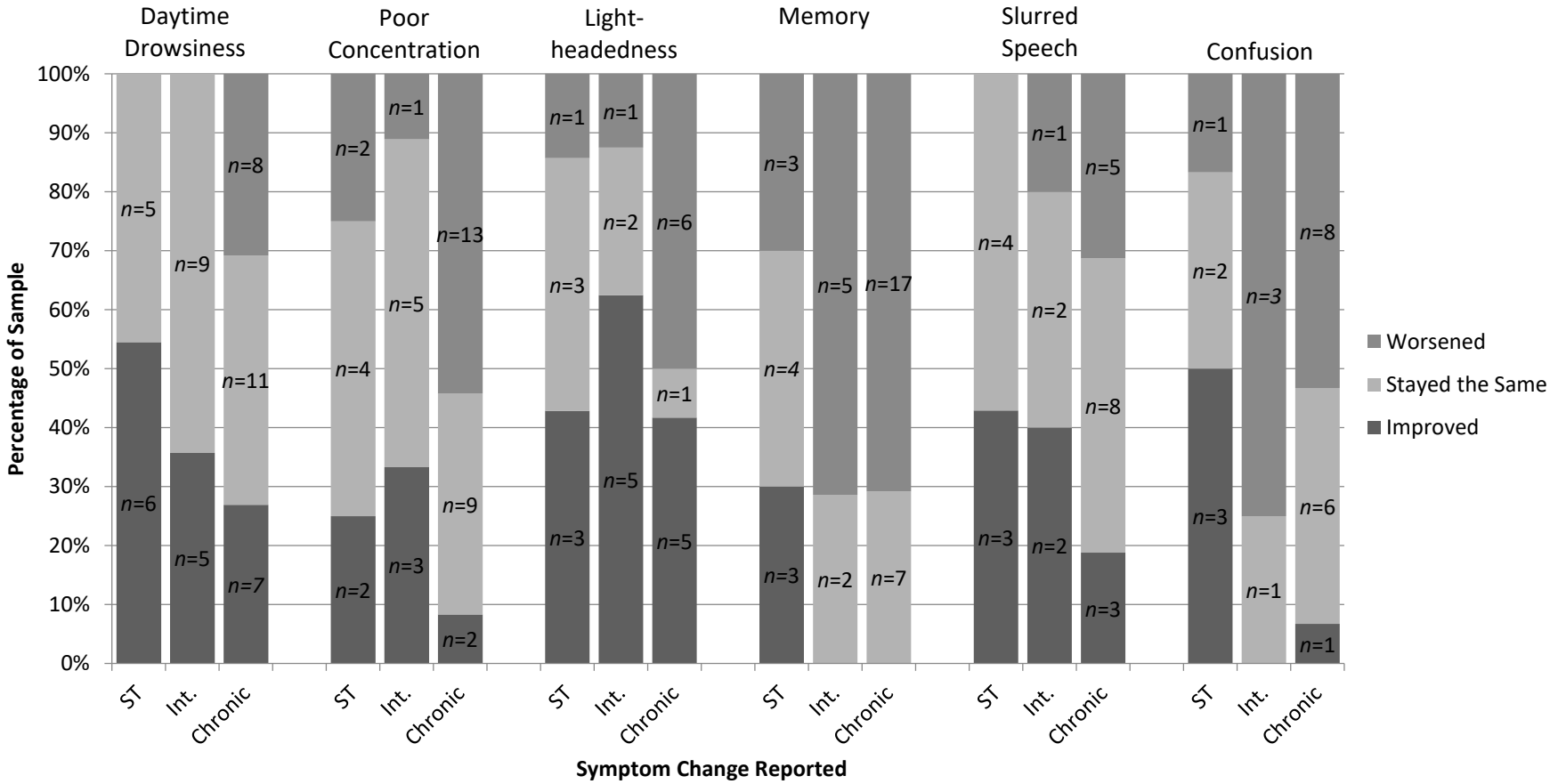

Figure 1. Symptom Change Experienced since Initiation of Benzodiazepine Use

Impact on Driving

Respondents were asked to identify the effect of benzodiazepine use on their driving ability, both when they initially started benzodiazepines and at the current time (Table 4). At both time points, over half the respondents in each group reported they detected no effect on driving ability. During initial use, and at the current time, the chronic users were most likely to report that using benzodiazepines worsened their driving ability. The sample was also asked if they took any precautions to keep themselves safe whilst driving; a range of precautions were listed to choose from (Table 4). The intermittent users were the most likely group to state either that they didn't take any precautions, or that they did not drive at all or immediately after they had taken a benzodiazepine. There were a variety of other precautions reported by respondents in the 'other answer' section including: *"I waited until I was aware of the effects and comfortable with the drug before driving on it", "I paid more attention to my surroundings",* and *"I minimised driving, I never drink any alcohol at all when driving, I plan my routes in advance to help with memory issues, I got a GPS to help with memory issues".*

Table 3. *Self-reported Impairment to driving ability in Benzodiazepine Users, at commencement of Benzodiazepine use and at current time, and Safety Precautions taken whilst driving.*

	Short-term Users (*n*=24)	Intermittent Users (*n*=55)	Chronic Users (*n*=50)
Initial detected impairment Survey Question: "*When you first started taking benzodiazepines (e.g. for the first month), how did you think they impacted on your driving ability?"*			
No effect	52.9% (*n*=9)	67.4% (*n*=31)	51.3% (*n*=30)
Worsened	17.6% (*n*=3)	13.0% (*n*=6)	30.8% (*n*=12)
Improved	11.8% (*n*=2)	2.2% (*n*=1)	12.8% (*n*=5)
Not applicable	17.6% (*n*=3)	17.4% (*n*=8)	5.1% (*n*=2)
Currently detected impairment Survey Question: "*How do you think your use of benzodiazepines currently impacts on your driving ability?"*			
No effect	62.5% (*n*=10)	60.9% (*n*=28)	68.4% (*n*=26)
Worsened	18.8% (*n*=3)	8.7% (n43)	21.1% (*n*=8)
Improved	6.3% (*n*=1)	8.7% (*n*=4)	7.9% (*n*=3)
Not applicable	12.5% (*n*=2)	21.7% (*n*=10)	2.6% (*n*=1)
Precautions[a] Survey Question: "*Whilst taking benzodiazepines have you taken any safety precautions in regards to driving?"*			
I did not take any precautions	20.8% (*n*=5)	30.9% (*n*=17)	30.0% (*n*=15)
I did not drive at all	25.0% (*n*=6)	29.1% (*n*=16)	8.0% (*n*=4)
I did not drive immediately after I had taken a benzodiazepine	25.0% (*n*=6)	27.3% (*n*=15)	20.0% (*n*=20)
I drove more slowly	12.5% (*n*=3)	12.7% (*n*=7)	14.0% (*n*=7)

[a]Two answer options are not listed in this table due to small numbers of participants identifying this as a precaution used: '*I stopped taking benzodiazepines'* (*n*=1) and '*I took other things to counter any side-effects'* (*n*=6).

Open Ended Questions

Respondents were initially asked to indicate whether they worried about using benzodiazepines. Percentages of each group reporting 'worry' are as follows: short-term users (68.4%, *n*=13), intermittent users (35.4%, *n*=17), and chronic users (43.2%, *n*=19). Respondents were then invited to comment further on this answer. Answers from two open-ended questions were organised into the following themes; addiction and dependence, ability to manage usage, withdrawal, stigma and availability, positive effects of benzodiazepine use, negative effects of benzodiazepine use, and provision of benzodiazepine information. For each theme, selected quotes that were a representative and/or an interesting example of this theme are presented.

Addiction and Dependence

Concerns about addiction to and dependence on, benzodiazepines emerged across all three user groups. Many respondents seemed aware of the risk of addictions, or had experienced this themselves, and made statements highly indicative of dependence:

> *They are highly addictive and it does scare me that eventually I will have to stop usage….Ch181*
>
> *I feel that the only reason I'm on benzodiazepines is that I can't stop. Ch224*
>
> *I often find myself thinking about them or wanting them, fully aware that they are not necessary. Int191*
>
> *It seems that my panic attacks have increased in frequency and intensity, and I end up popping a Xanax as I am scare to ride through the panic attack on my own. St71*

Several respondents indicated they felt unable to function normally without benzodiazepines:

> *I don't think I would be able to function normally without it. Ch55*
>
> *It felt essential that I took them. Ch59*
>
> *I find I cannot cope day to day without them. Ch181*

> *I'm glad I only used Diazepam for a brief time due to how much it can change you. St11*
>
> *I feel I am a prisoner of the drug…St73*

There was a concern, mostly amongst chronic users, that changing attitudes towards benzodiazepines would make access difficult. These opinions were also indicative of dependence, i.e. worry about how one would cope if availability was limited.

> *I worry that my doctor will cut off supply/I worry that there might be a disaster of some kind and I won't be able to get any. Ch58*
>
> *I have stockpiled some [Xanax] which should last me through until the end of 2014. Ch112*
>
> *I worry it will no longer be available in the future. Int49*
>
> *Worried that I will become addicted and not be able to get more. Int114*

Likewise some respondents identified that their use was recreational, or in excess of what they had been prescribed.

> *I've been using benzodiazepines recreationally for 18 months or so...In the last 6 months I've been using Xanax, oxazepam, temazepam, occasionally diazepam… Ch155*
>
> *…I can easily consume 100mg of diazepam and stay awake hanging out with my mates. Int191*
>
> *Realisation of how easy it would be to rely on the drug beyond what it's prescribed for. St11*
>
> *I'm only supposed to take it no more than once per day, but some days I need it twice. St52*

Ability to Manage Usage

Conversely, there were a few respondents, usually intermittent users, who reported they were able to limit their benzodiazepine use, or stated that they did not find them addictive.

> *I have yet to feel any addictive effect myself, but have watched others crave it as they would with smoking…Ch40*

> *I do not find this medication (diazepam) addicting or feel the need to use it in a recreational setting. Int49*
>
> *I only take it when needed, might be every day for a couple of weeks, sometimes none for months. Int233*
>
> *I know these drugs are addictive and would never use them more than rarely for that reason. Int234*

Withdrawal

Many of the respondents, particularly chronic users, reported difficulty withdrawing, fear of future withdrawals, and rebound symptoms when reducing use.

> *I have tried numerous attempts at dosing down in a tapering program to move me over to a lesser benzo such as Valium. Ch42*
>
> *I tried to wean off but failed. Ch140*
>
> *The withdrawal is far too painful and makes it very hard to get off it. Ch152*
>
> *…I started having really powerful withdrawal symptoms such as unbearable anxiety, depression, and feeling so out of it I didn't know if I was dreaming or awake. Ch218*
>
> *As someone now withdrawing my family has suffered watching the terrible side effects these medications can have, mood swings, and onset of depression after your last dose. St238*

Stigma and availability

Another theme that emerged was that benzodiazepine users often felt stigmatised for seeking benzodiazepines, even if their own use was within therapeutic guidelines.

> *Certain doctors are ignorant or morally opposed to prescribing me this horrible drug. Ch42*
>
> *The worst part for me is feeling like a criminal when I have to ask my GP for a repeat prescription. Ch47*
>
> *It is harder for valid patients to acquire their medicine. It is very effective for my ailments and as a patient I should not be penalised for others misuse. Int49*

Positive Effects of Benzodiazepine Use

There were some respondents who reported positive benefits of benzodiazepine use. Some respondents identified that benzodiazepines were efficacious in treating the conditions they were prescribed for. Others found they experienced minimal side-effects, or that the positive outcomes outweighed the side-effects they did experience.

> *I couldn't sleep without them. Ch62*
>
> *In my case, if I need PRN benzodiazepines, I believe the side effects (which in me are minimal), far outweigh the effects of anxiety and panic. Ch102*
>
> *I struggle daily with horrible panic disorder, depression, anxiety, and ADHD. Benzo's give me a release from this. Ch162*
>
> *I have been taking this medication for a long time, and do not feel that it affects me other than in a positive way. Ch205*
>
> *I have been on Xanax for over 25 years, and if it wasn't for this medication, I doubt I would be here today, due to the panic and anxiety attacks I have. Haven't had any real side effects from it, and only take it when necessary. Ch220*
>
> *The positives outweigh the negatives for me especially if I use them sparingly. Int63*
>
> *I do believe when I have an anxiety attack that the best way to fix it is with Diazepam. Int110*

Negative Effects of Benzodiazepine Use

Conversely, there were high numbers of respondents, particularly in the chronic user group, who reported negative side-effects, detrimental effects on health and well-being, and worry about the long-term consequences of benzodiazepine use.

> *Wrecks my motivation during the day and causes weight gain and my medication is only just holding for sleep. Not so happy. Ch231*
>
> *I have had no positive effects, I have only had negative side effects; physical, emotionally, financial and cognitively. Ch235*
>
> *Afraid clumsiness or lowered concentration can put me in danger while driving, crossing roads etc. Int151*

> *I'm worried that if I keep taking even the low dose I take I might get Alzheimer's. I think that my memory is not as good as it used to be. Int179*
>
> *It impacts on my ability to think clearly and feel. Int232*

Provision of Benzodiazepine Information

There was a small subset, of the chronic users only, who indicated feeling ill-informed about the potential ramifications of benzodiazepine use. Some of these respondents felt they had not initially been educated satisfactorily, whilst others reflected that in hindsight they would choose a different course of treatment.

> *I wish I had known then how very addictive these medications are. Ch47*
>
> *I wish that I had never taken them. Ch58*
>
> *I was prescribed these without any indication of what daily use could do. To be honest I think my prescriber was surprised to discover there was a withdrawal syndrome associated with them. Ch221*
>
> *I was placed on this drug almost seven years ago with no idea what it was or what the impact would be on my life long term. Ch235*
>
> *I believe I would have been better off never taking it to begin with. St71*

DISCUSSION

Results from this study reveal a group of people who for a variety of positive and negative reasons, rely strongly on benzodiazepines. This sample was categorised into three groups, and as expected, the groups differed on dose, duration, and frequency of use. Across all three levels of chronicity there were many who were using benzodiazepines in excess of the duration and frequency recommended by clinical guidelines. Attitudes to benzodiazepines were divided with many expressing that they wished to reduce benzodiazepine use due to the negative effects, but had difficulty in achieving this. Conversely, others felt that the positive benefits of using

benzodiazepines outweighed the negatives. Many of the most chronic benzodiazepine consumers felt they were not adequately informed about pros and cons of using benzodiazepines when they commenced the medication.

The self-reported reasons for use of benzodiazepines, in the majority did not clinically indicate the use of benzodiazepines as an ongoing treatment. Most of the sample reported that they were using benzodiazepines solely for sleep (*n*=59, 45.7%) or anxiety (*n*=54, 41.9%) problems, with only a small group reporting use for other or multiple reasons (*n*=16, 12.4%). When considering the treatment guidelines for anxiety and insomnia, cognitive behavioural therapy (CBT) is usually considered the first line treatment (Royal Australian College of General Practitioners, 2015b). Benzodiazepines are not indicated for mild to moderate anxiety, and are suggested be used only in situations where rapid symptomatic relief is required. In insomnia, benzodiazepines are suggested to be used only for short-term treatment (i.e. less than four weeks) and using the lowest possible dose (Royal Australian College of General Practitioners, 2015b). It is not known whether other treatments, such as CBT, have been utilised by this sample. However, the duration of benzodiazepine use in this group is far lengthier than what is usually recommended for the treatment of anxiety or insomnia. Even the most benzodiazepine-naïve group in the study, the short-term users, had an average length of use spanning almost six months, and on average they used about half the days in a month. The chronic user group had use spanning on average over 8 years, used most days in a month, and had an average monthly dosage of over 900mg (diazepam equivalent). Moreover, half the sample were within the high psychological distress range (K-10 score>21, *n*=51, 52%); the presence of these high scores may suggest that the treatment received by individuals (including benzodiazepines) is not adequately addressing their concerns. In this sample, the use of benzodiazepines is not concordant with common treatment guidelines, and their efficacy in providing symptomatic relief remains unclear. This raises the question of why use in this sample is so chronic, and how this can be more consistently managed.

Statements made by this sample were often indicative of benzodiazepine dependence, and a common obstacle to ceasing use, was experience, or avoidance of, withdrawal symptoms. Many individuals, particularly in the chronic and short-term user groups reported overwhelming symptoms of withdrawal including: '*mood swings*', '*seizures*' '*unbearable anxiety and depression*', '*ringing in the ears*', '*nausea*', '*light-headedness*', '*shaking*' and '*muscle twitches*'. There were some in the group who reported working on gradual dose reduction with their GPs, but many found this very difficult, and often relapsed at times of high demand. Evidently, many consumers in this study did not have the adequate resources to help them overcome withdrawal symptoms in order to cease benzodiazepine use.

A meta-analysis examining strategies that assist with benzodiazepine reduction, compared routine care (standard GP care plus assessment) with; brief interventions (such as provision of information pamphlets), gradual dose reduction, and psychological interventions, such as relaxation training and targeted cognitive-behavioural techniques (Parr, Kavanagh, Cahill, Mitchell, & Young, 2009). Both gradual dose reduction and brief interventions achieved higher cessation rates than routine care. The addition of psychological interventions to gradual dose reduction, was more effective than gradual dose reduction alone, at both cessation (OR 1.82, 95%CI 1.25-2.67) and follow-up (OR 1.88, 95%CI 1.19-2.97). There was little evidence to support the use of pharmacotherapy in benzodiazepine cessation. More recently, a scoping review (Pollmann, Murphy, Bergman, & Gardner, 2015), reviewed 139 articles that examined strategies used for deprescribing benzodiazepines. Deprescribing is described as a collaborative approach to discontinuing therapies that are no longer efficacious, or are doing the patient harm. Pharmacological interventions were the most common type of strategy reported in the studies reviewed (n=42 57%). Psychological strategies were studied in only 14% (n=10) of trials. Gradual dose reduction was included in 80% (n=60) of the discontinuation strategies. Over all of the strategies implemented, effects were mixed with 47% rated as having positive outcomes, 41% having negative outcomes, and 12% being mixed. The authors conclude that there is a lack of clarity in how

best to deprescribe benzodiazepines. Furthermore, they report that the outcome of interest in these studies is most commonly whether the benzodiazepine has been ceased, and other clinical outcomes, such as reduced falls risk, or improved quality of life, are less frequently investigated. These findings illustrate that benzodiazepine deprescribing is not approached consistently, nor are the most efficacious techniques, researched and provided the most intently. .

One barrier to deprescribing is the capacity of the clinician to deliver the most efficacious intervention. For example, it is possible that for GPs, providing deprescribing interventions may be beyond their scope and practical capacity. Considering this, research is increasingly looking to alternative ways to support benzodiazepine cessation; for example, recent research examined the impact of direct to consumer education material (Martin & Tannenbaum, 2017; Tannenbaum, Martin, Tamblyn, Benedetti, & Ahmed, 2014). The resource used in this instance was the 8-page EMPOWER booklet, which documented benzodiazepine safety information, inspiring peer stories, suggestions for alternative treatments, and gradual tapering instructions. In the initial trial (Tannenbaum et al., 2014), participants included 303 long-term benzodiazepine users (aged 65-95 years), recruited through a pharmacy; of these, 148 participants were mailed the information booklet, the rest formed the control group. At the 6 month follow-up, only 5% of the control group had discontinued benzodiazepines, whilst 27% of the intervention group had discontinued benzodiazepines (adjusted OR 8.3, 95% CI 3.3—20.9), and another 11% had achieved dose reduction. There were also other promising results, for example 62% of those who had completed the trial had initiated conversations about benzodiazepine discontinuation with their doctor or pharmacist. A later follow-up study (Martin & Tannenbaum, 2017), examined whether cognitive capacity affected the efficacy of the EMPOWER education brochure. From the initial trial, 261 participants continued this phase of the research, and all patients, including the previous control group, were given the EMPOWER brochure. Participants were divided based on their scores on the Montreal Cognitive Assessment, as having either normal cognition or mild cognitive

impairment (MCI). Follow-up data was collected one week, six weeks and 6 months after each participant received the brochure. Discontinuation was achieved in similar rates in both groups; 38.1% in the normal cognition group, and 32% in the MCI group (adjusted OR 0.79%, 95%CI 0.45-1.38). The MCI group showed the same capacity to change their beliefs related to benzodiazepine use, and to initiate conversations with their health care providers. The authors conclude their findings indicate that clinicians should be encouraged to use the EMPOWER brochure to assist with benzodiazepine cessation, including in patients with cognitive decline. Overall this type of research shows that utilising clever, and complimentary interventions can have a positive effect on benzodiazepine reduction, and overcome some of the barriers to traditional benzodiazepine deprescribing. These types of interventions also encourage the involvement of other health professionals, such as pharmacists, whose role in benzodiazepine deprescribing in Australia is mostly medication management, and patient education. In this sample, common misconceptions about the efficacy of benzodiazepines, also seemed to lead to their overuse. Some patients identified that they felt benzodiazepines were the best option to manage symptoms, for example *"I do believe that when I have an anxiety attack that the best way to fix it is with Diazepam, although it's not always available for me to do so."* Many also identified that they lacked other ways to cope, particularly ones that are as seemingly efficient as benzodiazepines. A similar theme, described as 'the purpose and importance of benzodiazepines' was found in a comparable qualitative study (Cook, Biyanova, Masci, & Coyne, 2007). The study of 50 older adult benzodiazepine users (age range 61-95 years), identified that many in the sample described benzodiazepines as necessary to maintaining normal life, and these patients anticipated that their quality of life would be much poorer without benzodiazepines. A parallel study by the same authors, examined the attitudes of GPs (*n*=33) to prescribing benzodiazepines for older adults; similar beliefs emerged for both patients and physicians. GPs tended to minimise the problems associated with benzodiazepine use, and justified their ongoing use, particularly with the emphasis that in older patients, discontinuation causes undue suffering, with little benefit (Cook, Marshall, Masci, & Coyne, 2007). In a similar

study looking at the attitudes of GPs initiating new scripts, it was found GPs often felt overwhelmed by the patient's psychosocial problems, felt there was a lack of other viable solutions, and thus prescriptions were driven by a need to help (Anthierens et al., 2007). In both these studies, and the current one, similar feelings of helplessness seem to emerge for both the prescriber and patient.

In light of these findings, it seems necessary that both prescribers, and in turn patients, are educated on the limitations of benzodiazepine use, and the efficacy of alternative treatments. For example, CBT is established as an effective, and first line treatment for various mental health conditions (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012), and often has improved efficacy compared to benzodiazepines, and certainly less side-effects (Mitchell, Gehrman, Perlis, & Umscheid, 2012). Quality standards developed by the National Institute for Health and Care Excellence (NICE), aim to improve the outcomes of care in areas identified as needing quality improvement. For example, in relation to anxiety, the NICE standard recommends the use of psychological interventions as first line treatment in preference to pharmacological treatments (National Institute for Health and Care Excellence, 2014). These evidence based standards can be used by medical practitioners to guide best practice around prescribing benzodiazepines, and most importantly encourage the use of the least intrusive, and effective interventions. Whilst the limitations of benzodiazepines must always be communicated perhaps what is lacking is adequate endorsement regarding the relative efficacy of psychological interventions.

A brief investigation revealed overall the sample was not very knowledgeable about the potential side-effects of benzodiazepines. This is surprising given many of the group have been using for multiple years, and thus should have been exposed to this information on a number of occasions. The least commonly reported source of regulated information was the medication warning label on the box. Within Australia, benzodiazepines are required to be dispensed with a specifically worded sedation warning label on the box, with the aim of increasing consumer caution, and thus reducing accident risk. Unfortunately, it appears that the tendency for

medication labels to pass unnoticed or not be understood, decreases their efficacy. Recent research that tracked eye movements whilst participants studied a medication vial, explored how the action of noticing or attending to a label, was associated with later remembering this information (Sundar, Becker, Bello, & Bix, 2012). It was found that during viewing, participants often failed to fixate on the prescription warning labels. Regardless of age, subjects were more likely to later recognise the labels if they had fixated on them earlier (p=0.02). However, attention to a warning label is irrelevant if that information cannot then be understood. An Australian population literacy survey indicated that almost 60% of Australians aged 15 to 74 do not have the necessary literacy skills to understand health information such as medicine labels (Australian Bureau of Statistics, 2008). Ley (1995) examined existing research on medicine warnings and directions, and concluded that medication labels are noticed on average by only 50% of people, that only 20% of people read beyond the first line of the warning, almost 25% of warnings are not understood by their target audience, and only about 50% of people actually heed the warning or caution. There is some evidence that simplifying warning information, and adding pictorial explanations may assist with understanding medication labels. A study of 500 adults in the USA, aimed to explore how understanding of medication labels differed across three methods of delivery – standard drug warning labels, simplified text, and simplified text plus pictorial icons (Wolf et al., 2010). It was found that compared to the standard warning labels, there was a significantly increased frequency of correct interpretations for labels with both simplified text (adjusted OR 2.64, 95%CI 2.00-3.48) and simplified text plus icons (adjusted OR 3.26, 95%CI 2.46-4.32). For people with low literacy the use of simplified information plus pictorial icons was associated with improved understanding of labels, compared to labels with simplified information only (adjusted OR 3.22, 95%CI 139-7.50). The final element of efficacy for these warning labels, is whether they result in any meaningful behaviour change. Very recently, a study in France (Orriols et al., 2016) examined the impact of changed medication labelling on the association between benzodiazepines and z-drugs, and accident risk. Over the last decade in France, a coloured pictogram medication label has been

implemented, which indicates one of four levels of risk in terms of a medication's effect on driving performance. For the study, data were extracted from 3 French databases and included 69,353 responsible and 73,410 non-responsible drivers involved in traffic accidents. The association between benzodiazepine use and accidents was examined at four time points; prior to the pictogram introduction (2005), during the initial use of the pictogram (2007), and at two time points post pictogram introduction (2008 and 2010). Benzodiazepine anxiolytics were associated with an increased risk of responsibility for traffic accidents during the pre-intervention period (OR 1.42 95%CI 1.24–1.62). This association disappeared during the time of the pictogram implementation (OR 1.08, 95%CI 0.93-1.26), but became significant again at the two post-intervention time points (2008; OR 1.19, 95%CI 1.03-1.37 and 2010; OR 1.35, 95%CI 1.18-1.54). The authors concluded that the sizeable impact of benzodiazepines on traffic accident risk, warrants the attempt to improve medication labelling. However, in the French study, there were minimal effects of the pictogram in reducing accident risk, and the authors question the efficacy of this as a safety measure. In summary, various research indicates that there are several barriers to the efficacy of medication warning labels in reducing harm. This is affirmed by the current study where medication warning labels were rarely identified as a source of medication knowledge. Changes to medication labelling in Australia have been gradual, but it is suggested that as with the French study by Orriols et al. (2016) any changes should be accompanied by robust research that establishes whether changes to warning labels result in a subsequent reduction in harm.

The number of respondents that reported health professionals as a source of information about negative side-effects was also limited, with only about one third of each group reporting they were informed by their doctor, and approximately one-fifth by the pharmacist. Likewise, in response to the open-ended questions, some individuals identified they did not feel adequately informed about the potential risks and side-effects of using benzodiazepines. Similar findings occurred in earlier mentioned sample of older adults, most of whom reported that their

doctors had not discussed the negative side-effects of benzodiazepines, which in turn was taken to imply the implicit approval of the doctor in the safety of benzodiazepines (Cook et al., 2007). It is not clear from the current data whether these low figures are an accurate indication that this education is not taking place, or whether it has occurred but been dismissed or forgotten – perhaps due to the memory impairing effects of benzodiazepines. Either way, it must be ensured that key benzodiazepine information is provided to, and retained by patients. With estimates that 40-80% of medical information provided to patients is forgotten immediately (Kessels, 2003), it is clear that steps must be taken to circumvent this. Evidence suggests the provision of both oral and written basic information, aids recall (Kessels, 2003). With respect to benzodiazepine prescriptions, it is suggested that standardised, consumer-friendly, written and pictorial information should be *required* to be provided. This should be provided firstly by the prescriber to ensure the patient is fully informed before the prescription occurs, but should be also be supported by pharmacists. Evidence shows that patient outcomes are improved when prescribers and pharmacists work together collaboratively (Pharmacy Guild of Australia, 2012; Zillich, McDonough, Carter, & Doucette, 2004). These processes would ensure firstly, that benzodiazepine information is provided consistently, and secondly, that the likelihood of recalling this information is maximised.

Despite a low level of knowledge about side-effects, it was not unusual for the group to experience these symptoms. The short-term and chronic users were more likely to report that they had experienced a range of common side-effects (daytime drowsiness, poor concentration, light-headedness, memory loss, slurred speech, and confusion). For some individuals these side-effects did not abate as use continued. Differential development of tolerance to benzodiazepines occurs, although it is not fully understood; tolerance to the anticonvulsant and hypnotic effects occurs relatively quickly, and tolerance to the anxiolytic and amnestic effects occurs more slowly, if at all. However, self-reported experience of side effects indicates that for many, tolerance has not developed completely to benzodiazepines. Current recommendations suggest that any ongoing use of

benzodiazepines should occur only with regular cost-benefit analyses (Royal Australian College of General Practitioners, 2015b). Experience of these adverse side-effects should be a trigger for health professionals to engage in this discussion, and any ongoing benzodiazepine use should be accompanied by increased clinical observation (Royal Australian College of General Practitioners, 2015b).

The main concerns that arise from this study, are that benzodiazepine use is often far from best practice, and that users are not always thoroughly educated as to the potential negative effects of benzodiazepines. When considering the solution to these issues, it is evident that there are many good recommendations that already exist (Royal Australian College of General Practitioners, 2015a, 2015b). Unfortunately, in the main, these are non-mandated policies and implementation is left largely to the individual, or organisation, with varying outcomes. A recent meta-analysis by Sirdifield and colleagues found a number of factors, such as patient characteristics and GP attitudes to other treatments, have led to general practitioners' "ambivalent attitudes" and "inconsistent management strategies for prescribing benzodiazepines" (Sirdifield et al., 2013: p.6). It seems that what is required, is to draw the large body of benzodiazepine literature into a legally and professionally binding protocol, for the improved management of benzodiazepines.

It is proposed that one approach to standardising benzodiazepine prescription could include replicating the opiate contracts that are typically used in the management of pain relief (Queensland Government Drug Dependence Unit, 2010). The aim of medication contracts is to ensure that both patient and doctor have effectively communicated regarding the risks and benefits of a medication. There have already been attempts to modify contracts for benzodiazepine use, for example the recent Royal Australian College of General Practitioners' guidelines (Royal Australian College of General Practitioners, 2015b); this contract, whilst thorough, may be too complex for day to day use. A proposed alternative is provided in Table 4, this has been modified from the Queensland Government Opiate contract, and in light of the low health literacy identified in Australia (Australian Bureau of Statistics, 2008) the language simplified (Queensland Government Drug Dependence Unit, 2010).

Whilst opiate contracts usually focus on dependence risk, the findings of this research illustrate the importance of additional considerations in a benzodiazepine contract. It is suggested that a benzodiazepine contract should particularly facilitate the opportunity to have open discussion regarding the limitations of benzodiazepines, specifically the risks associated with ongoing use, and the discussion of alternate treatment approaches, such as CBT. Benzodiazepine contracts could also be used in conjunction with a real-time reporting system, which would not only reduce issues like doctor shopping, and high risk drug interactions, but would also provide quick transfer of information to other health professionals.

Table 4. *Proposed Benzodiazepine Medication Contract to assist with Maintaining Therapeutic Usage.*

UNDERSTANDING BENZODIAZEPINES

I, *(name)* _____ understand that a benzodiazepine is being prescribed to help me with my:

(insert presenting problem) _____

_____.

- ☐ I understand that benzodiazepines may only be one part of treating this condition
- ☐ My doctor and I agree to the following ideas about my use of benzodiazepines:

Prescription

- I will only take the benzodiazepine at the dose stated by my doctor. I will not change my dosage without talking to my doctor first. My dosage is:
  _____
  _____
- I need to keep my benzodiazepines safe. Lost or stolen prescriptions or medicine will not be replaced by my doctor.
- I will only get benzodiazepine scripts from the doctor who signs this contract, or other doctors in the same practice (if agreed upon).
- I understand that I cannot have early prescriptions.

- I agree to tell my doctor if I have ever had a problem with alcohol or drugs, or if I have ever been involved in illegal activity related to any drugs including prescription medicines.
- I know that giving my medicine to other people is illegal and could be unsafe for them.

Side-effects and long-term consequences

- My doctor respects my right to make choices about my condition and will explain the risks, benefits, and side effects of any treatment.
- Most people do not have any serious problems with benzodiazepines when used as directed, but there can be side effects. My doctor has said what these are, and given me a copy of them in writing, and I will tell him or her if I experience them.
- I understand that using benzodiazepines for more than 4 weeks could affect my health. For this reason my doctor and I will work on other ways of treating my condition.

Treatment Plan

- My doctor will keep reviewing the symptoms that I have. I will make another appointment by the *(date)*_____ to review my progress.
- I understand that benzodiazepines are best for short-term use only. My doctor and I have talked about other ways of managing my symptoms. The next steps I will take to find other treatments are:

  _____

  _____

  _____

  _____

- My doctor and I will discuss the ongoing risks and benefits of using benzodiazepines. If we decide they are no longer helpful, or if I fail to abide by this contract, they may stop prescribing benzodiazepines or change the treatment plan.

Patient Signature:_____

Name: _____Date: _____

Medical Practitioner Signature: _____

Name: _____Date: _____

It is not uncommon for both research and popular media to focus on the negative aspects of using benzodiazepines. It is less often acknowledged that there are those who are able to use benzodiazepines 'as required' and to stop using them without problems (Baldwin et al., 2013). There was such a group of patients in the current study, often the intermittent users, who reported that the benefits of benzodiazepine use outweighed any negatives, that they were able to use only occasionally, and that they received symptomatic relief. Benzodiazepines were described as *'the only thing that helps', 'effective and safe'*, and even *'life-saving'*. Nevertheless, many patients reported that they felt stigmatised when seeking a benzodiazepine prescription. Despite the highly negative publicity regarding benzodiazepines, it is vital health professionals remain aware that many patients receive genuine benefits from using benzodiazepines. Standardised procedures for all patients seeking benzodiazepines would reduce the likelihood of any individuals feeling stigmatised.

The major limitation of this study is that it explorative in nature; a more rigorous qualitative approach would allow increased confidence in the themes that have been identified. However, the study does add to the substantive body of experimental benzodiazepine research, by adding often missed information about the views and experiences of benzodiazepine consumers. Recently, there has been growing recognition that quantitative and qualitative research methods, can be complementary rather than exclusive (Pope, van Royen, & Baker, 2002). In this study, themes were developed out of the respondents' open-ended responses. Because development of themes occurred post-data collection, it became evident at this time that extra information would have helped to inform and explain some of these research themes. For example, a commonly identified theme was that respondents' struggled with withdrawal symptoms. In order to better understand this, information about interventions received (e.g. gradual dose reduction, or psychological interventions) would have helped to clarify respondents' experiences. Despite this, the aim of the open-ended questions was to be exploratory in nature.

Some of the themes identified by this research could form the basis for a more detailed area of study.

Results of this study suggest there is a population of chronic benzodiazepine consumers who are using for durations and dosages far beyond clinical guidelines. Whether benzodiazepines remain efficacious in this group is undetermined, but unlikely. Emerging from this study were three key opportunities to intervene with benzodiazepine users - currently it is not clear whether these interventions consistently occur in a meaningful way. Firstly, many individuals reported that they felt inadequately informed about the risks when beginning benzodiazepines. Providers of this information need to account for the amnestic properties of both benzodiazepines, and the conditions for which they are prescribed – information needs to be provided repeatedly and in both written and oral forms. Secondly, many of the respondents experienced side-effects of benzodiazepines. Continuing use of benzodiazepines should always be accompanied by ongoing discussions of risks and benefits, and reporting of side-effects can be used as a cue for such discussions. Finally, withdrawal symptoms were identified as a significant barrier to cessation of use, those wishing to reduce benzodiazepine use should be provided with both gradual dose reduction, and alternative coping techniques. Despite benzodiazepine guidelines being first implemented over 35 years ago (Committee on the Review of Medicines, 1980), it seems that they are not regularly adopted in practice. Currently there are comprehensive, evidenced-based guidelines available to direct prescription of benzodiazepines (Royal Australian College of General Practitioners, 2015a, 2015b). It seems what is lacking is a standardised application of these guidelines. It is proposed that a benzodiazepine medication contract could be used to guide both prescribers, and patients in the safe use of benzodiazepines.

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9 General Discussion

CHAPTER 9: GENERAL DISCUSSION

The focus of this thesis was to investigate the relationship between benzodiazepine use of varying chronicity, and experience of safety incidents. The first study investigated benzodiazepine use in a general population. Benzodiazepine use was classified as short-term, intermittent, or chronic. Experience of incidents was explored across a continuum including cognitive failures, minor injuries, and major accidents. The second study explored the unique effects of chronic benzodiazepine use on safety, in a group of people who inject drugs (PWID). PWID are a population group already at a high risk of safety incidents, due to risk factors such as particular demographic characteristics and the impairing effects of polydrug use. It was found that in both the general population and PWID, benzodiazepine use was uniquely and independently associated with a higher risk of safety incidents. In the third study, the subjective experiences of regular benzodiazepine users were investigated. There was a focus on how the perceptions and attitudes of benzodiazepine users varied with different chronicity of use. The research questions and relevant findings are summarised below (Table 1).

Research Findings

Table 1. *Core Research Questions and Related Findings and Conclusions*

Research Question	Chapter(s)	Key Findings *(^{u}=Finding significant in univariate results only; ^{m}=Finding remained significant in multivariate results)*	Conclusion
What are the associations between ongoing benzodiazepine use and various incident types – in the general population and people who inject drugs (PWID)	6,7	*General Population Sample:* Chronic benzodiazepine users experienced increased rates of general accidents^{m}, retrospective memory^{m}, and prospective memory problems^{u}. A high monthly dose of benzodiazepines was associated with increased risk of traffic accidents in the last 12 months^{u}. *PWID:* Regular benzodiazepine users experienced significantly more major accidents^{m}, and retrospective^{m} and prospective memory^{u} problems than low use users.	Benzodiazepine users are at an increased risk of safety incidents, after controlling for a variety of other demographic, health and drug use variables.
Is benzodiazepine use associated with each of the incident types listed above in the same way, or are some incident types more susceptible to benzodiazepine use?	6,7	Benzodiazepine users experienced increased rates of cognitive failures and major accidents. No significant effects associated with benzodiazepines were found for minor accidents.	Benzodiazepine use did not affect all incident types uniformly. Minimal prompting and poor recall of minor injuries may have affected findings.

Research Question	Chapter(s)	Key Findings *(^{u}=Finding significant in univariate results only; ^{m}=Finding remained significant in multivariate results)*	Conclusion
What effect does chronicity of benzodiazepine use have on experience of incident types?	6,7	Comparisons between three categories of benzodiazepine chronicity showed chronic users had higher rates of incidents than intermittent users. There were no differences between chronic and short-term users	Pattern of benzodiazepine use is important. Long-term, daily users were the most likely to experience problems.
Is experience of incidents associated more strongly with dosage, or pattern (duration and frequency) of benzodiazepine use?	6,7	Dosage had a significant effect on two variables only; traffic accidents in last 12 months^{u} and prospective memory^{u}. Chronic benzodiazepine use was associated with a broad range of incident types in both the general population and PWID.	Chronic benzodiazepine use is an important target for harm reduction.
What do regular consumers know about the side-effects of benzodiazepines?	8	Only 3.1% (*n*=3) of the entire sample, were able to correctly identify 10 side-effects of benzodiazepines.	Knowledge of common benzodiazepine side-effects is poor, even in those who have been using for some time.
From what sources is information about side-effects obtained?	8	The most commonly reported source of information for all groups was 'the information in the box' Low numbers of respondents reported they had received information from their doctor or pharmacist	Steps should be taken to ensure information is provided routinely, and information should be provided in both verbal and written format to maximise recall.
What detrimental effects do benzodiazepine consumers detect?	8	Short-term and chronic users most commonly reported experience of negative side-effects, and often did not experience a resolution of symptoms. Approximately half the sample reported no effect of benzodiazepines on their driving ability. Chronic users were most likely to report using benzodiazepines worsened driving ability.	Despite many of the sample reporting they experienced continuing side-effects, subjective benzodiazepine-related impairment on driving ability was not noted consistently across the cohort. It is possible this may be an effect of impaired meta-cognition (e.g. the ability to detect impairment).
Do people take any precautions regarding benzodiazepine use and driving?	8	Most commonly, the sample did not implement any precautions whilst driving. The most common precautions used were not driving at all, or immediately following, benzodiazepine use.	Precautions reported by the sample were sensible, with many choosing not to drive when using benzodiazepines. This may be the reason few respondents reported impairment to driving ability (see above).

Research Question	Chapter(s)	Key Findings *(^{U}=Finding significant in univariate results only; ^{m}=Finding remained significant in multivariate results)*	Conclusion
What are the general worries and concerns that regular benzodiazepine consumers experience (related to their benzodiazepine use)	8	Open-ended questions were organised into the following themes: Addiction and dependence, ability to manage usage, withdrawal, stigma and availability, positive effects of benzodiazepine use, negative effects of benzodiazepine use, and provision of benzodiazepine information.	Many of the sample reported symptoms indicative of benzodiazepine dependence. Withdrawal symptoms were a significant barrier to ceasing use. Whilst many of the cohort reported negative experiences of benzodiazepine use, there was also a small group who reported that using benzodiazepines had a generally positive effect. Many reported regularly feeling stigmatised, when seeking benzodiazepine prescriptions.

Outcomes from the General Population Sample

Reported benzodiazepine use within *Study 1 and 3* was high. Data from the general population indicated dose, frequency, and duration of benzodiazepine use was often chronic in nature. This is despite clinical guidelines repeatedly emphasising that benzodiazepines should be used *at the lowest effective dose,* and for *the shortest time period possible* (National Health and Medical Research Council, 1991; Royal Australian College of General Practitioners, 2015b). Recent Australian studies indicate that benzodiazepine use has plateaued over the last 20 years (Hollingworth & Siskind, 2010; Islam, Conigrave, Day, Nguyen, & Haber, 2013; Stephenson, Karange, & McGregor, 2013). However, population utilisation still remains high, and statistics may be affected by the popularity of different formulations at different times, and a move towards larger quantity private prescriptions (Islam et al., 2013). Whilst these population trends show a decrease in Australian benzodiazepine use, data from the current study indicates that at the individual level, there are still many who use in a manner contrary to clinical indications.

Symptoms reported in the qualitative study were often consistent with benzodiazepine dependence, for example, many reported escalating benzodiazepine use and strong withdrawal symptoms. Lader (2011) suggests there are two main groups of people who become benzodiazepine dependent; those who are initially prescribed benzodiazepines to manage symptoms and then are maintained on the dose by prescribers (involuntary/iatrogenic dependence), and then those who actively seek benzodiazepines for intentional abuse of their psychotropic properties. Of those involved in the current studies, there are most certainly some that fall into each category. This chronic and dependent use of benzodiazepines indicates that there are shortfalls in the procedures surrounding the management of both licit and illicit benzodiazepine use.

Whilst benzodiazepine use in the general population sample was high, information from the qualitative study suggests that many did not want to be using at this frequency. Many of the respondents communicated a desire for their

benzodiazepine use to be different, but had difficulty achieving this, and expressed comments such as: *"I feel that the only reason I'm on benzodiazepines is that I can't stop", "I wish that I had never taken them",* and *"the withdrawal is far too painful and makes it very hard to get off it*". What these patients are describing is ambivalence about continued benzodiazepine use. Ambivalence is a key concept in the motivational interviewing framework (Miller & Rollnick, 2012), which emphasises using a patient's own conflicted feelings or attitudes to encourage change. The times when patients express dissatisfaction about benzodiazepine use, are key opportunities to start a discussion about the risks and benefits of continuing use. Unfortunately, despite the ambivalence about continuing benzodiazepine use that many of this cohort report, it seems that they are lacking the support to progress with their withdrawal from benzodiazepines.

Evidence from all three studies indicated that those who use benzodiazepines in the most chronic manner, were at the greatest risk of negative consequences. Chronic users experienced more safety incidents and self-reported more negative symptoms, compared to those who used only intermittently over the same time period. Chronicity of use had a greater association with safety incidents than the dosage used. These findings are at odds with the commonly held belief that regular users of medications become tolerant to all of the effects of that medication. It is known that the development of tolerance to benzodiazepines develops differentially; developing quickly for some effects, e.g. hypnotic and anticonvulsant effects, and more slowly or not at all for others, e.g. anxiolytic and amnestic effects (Vinkers & Olivier, 2012). Evidence from the current study suggests that long-term benzodiazepine users do not develop tolerance to many of the problematic side effects of benzodiazepines. This was evidenced both objectively, through the elevated experience of safety incidents, and subjectively, through the report of continued negative effects. Practically, this indicates that chronic benzodiazepine users do not become immune to the risks of using benzodiazepines, and that they should be regularly reminded of this by health professionals. Requests for repeat prescriptions should be a prompt to discuss the risks and benefits of continued use.

Given that chronic users experienced increased incidents when compared to intermittent users, there is some indication that a reduction in frequency of use may be a valuable harm reduction technique. This is also consistent with guidelines that recommend regular breaks in benzodiazepine dosing to reduce the likelihood of dependence (Royal Australian College of General Practitioners, 2015b). However, it must be acknowledged that this places high demands on the practitioner managing the withdrawal, who may often not have originally initiated the prescription. More specialised services may be required to meet these demands.

Outcomes from the PWID sample

In the sample of people who inject drugs, almost one-third of the group had used benzodiazepines daily for at least the last six months. Clinical guidelines recommend against the prescribing of benzodiazepines to people who misuse both legal and illegal drugs, due to the high risk of adverse events occurring. When benzodiazepines are combined with other depressant drugs, such as alcohol or opioids, there is a risk of central nervous system depression, which can result in injury or death (Jones, Mogali, & Comer, 2012). Additionally, people who have previously misused drugs, are at a greater risk of becoming problematic benzodiazepine users (Tvete, Bjorner, Aursnes, & Skomedal, 2013). As such it is recommended that benzodiazepine use is not initiated in polydrug users, and that if they are already using benzodiazepines then cessation of use should be a priority (Royal Australian College of General Practitioners, 2015b). Despite these recommendations, benzodiazepine use within the PWID cohort was high, though it was not clear whether benzodiazepines were obtained from licit or illicit sources.

Finding regular benzodiazepine use in high risk populations is not uncommon. The National Opioid Medication Abuse Deterrence (NOMAD) project examined the use of major drug types, before and after the introduction of an abuse deterrent sustained-release oxycodone formulation (Reformulated OxyContin®). In one sample resulting from the NOMAD study, 606 people who regularly tamper with pharmaceutical opioids were examined (Degenhardt et al., 2015). Before the

introduction of the Reformulated OxyContin®, 72% of the cohort had used benzodiazepines in the past month. Post-introduction there was a reduction in use of most types of opioids and a statistically significant decrease in the use of benzodiazepines, with 66% reporting benzodiazepine use in the past month. Despite the downward trend, benzodiazepine use in this group was extremely high at both time points.

Similarly, the Pain and Opioids in Treatment (POINT) project, examines those who use prescribed opioids for the management of chronic non cancer pain (CNCP). Again, use of benzodiazepines in this group is contraindicated, due to low efficacy in treating symptoms, and a high risk of complications through drug interactions. In a sample of 1,220 CNCP patients, the group was evenly divided between those who had never used, who had previously used, or were current benzodiazepine users (Nielsen et al., 2015). In the one-third (33%) of the group that had used a benzodiazepine in the past month, 53% were using daily. Benzodiazepine use was associated with poorer health outcomes and high utilisation of health services.

Findings from these studies, show three cohorts who are high risk benzodiazepine users; people who inject drugs (current study), illicit opioid users (NOMAD study; Degenhardt et al., 2015), and prescribed opioid users (POINT study; Nielsen et al., 2015). Research into the concomitant effects of benzodiazepines and opioids first occurred in the 1970s (Kleber & Gold, 1978). Continually, the association between combined benzodiazepine and opioid use, and increased harm has been established; for example increased risk of overdose (Darke, Ross, & Hall, 1996) and poor mental health (Eiroa-Orosa et al., 2010). Many years on from the initial research, there are clear recommendations to limit the use of benzodiazepines in these high risk groups. However, research in multiple cohorts, including the current one, shows the prevalence of benzodiazepine use in these populations is still extremely high. What is evident from these findings is that the quality prescribing of benzodiazepines is failing, in both general and high risk populations.

The Incident Continuum

One of the aims of this thesis was to include safety incidents with varying severities, in order to comprehensively explore the effects of benzodiazepines on safety. These incidents included accidents requiring medical attention, minor injuries, and cognitive failures. In both the general and PWID populations, there were significant effects of benzodiazepine use on major accidents and cognitive failures. However, no significant associations were found between benzodiazepine use and minor injuries. Whether this lack of association is a valid finding, or resulted from some bias in reporting is unclear. The reporting of minor injuries could be influenced by individual differences related to recall, definition, and saliency of events. However, incidents occurred in the current general population sample at comparable rate to a UK population sample (Wadsworth, Moss, Simpson, & Smith, 2005); and as expected incident rates were significantly increased in the PWID sample. This suggests that there was not consistent under-reporting of incidents that occurred in the current samples. The survey questions related to minor injuries were taken directly from the work of Wadsworth and colleagues (e.g. Wadsworth et al., 2005). However, the use of this question (e.g. 'in the last 12 months how frequently have you had minor injuries (e.g. cuts and bruises) that did not require medical attention from anyone else?') is quite non-specific and requires the participant to make a decision about what constitutes a minor injury. Future research examining minor injuries may benefit from the development of a specific measurement tool. For example, the Prospective Retrospective Memory Questionnaire (Crawford & Smith, 2003) used in this thesis, asks respondents to indicate how often they experience particular specific memory failures. A similar format, providing specific examples of minor injuries, may help respondents with recognition and recall. The accurate identification of minor injuries, may also be aided by the use of real-time technology. For example, a phone App could be used to prompt study participants to record any safety incidents that they experienced, at regularly occurring intervals. Real-time technology may also allow the exploration of relationships between the different incident types. There is some evidence that shows

associations between cognitive failures, and accidents (Larson, Alderton, Neideffer, & Underhill, 1997; Simpson, Wadsworth, Moss, & Smith, 2005), and it has been suggested that context or environment may influence whether or not a cognitive failure results in an accident (Simpson et al., 2005). However, further research is needed to better understand the causative relationships between cognitive failures, minor injuries, and major accidents.

Strengths, Limitations, and Recommendations for future research

A considerable strength of the current studies is that they examine benzodiazepine use within the context of other potentially confounding variables. Much of the existing benzodiazepine literature examines carefully crafted research samples – study respondents are often benzodiazepine-naïve individuals, with no other health conditions, or drug use. This does not allow the unique and potentially additive effects of benzodiazepines to be explored. In both the general and PWID samples, there was an array of variables that were associated with safety incidents. It is notable that even in the context of high severity injecting drug use, some substances that may be considered a low treatment priority, such as alcohol and cannabis, had significant associations with safety. This demonstrates that people who use benzodiazepines often have many factors that influence their health and well-being. From a harm reduction viewpoint, this highlights the importance of screening for, and reducing polysubstance use, even for legal substances such as alcohol and benzodiazepines. The main limitation of the general population study, was that despite varied participant recruitment methods, the sample size was small. Whilst trends emerged in this sample, a larger sample would allow these findings to become clearer. In hindsight, the survey length may have been too onerous for respondents, and therefore affected completion numbers. Also whilst there was the aim to capture a general population sample, it is possible that responder bias occurred. Specifically, those that completed the survey may have been compelled to do so due to a strong positive or negative sentiment towards benzodiazepines. Certainly, in the responses to the open-ended questions, polarised opinions towards benzodiazepines were evident. The current sample was also quite

weighted towards long-term benzodiazepine use; even the short-term user group had an average use that spanned 168 days. This may in part also have been due to a responder bias, where those who had only been using benzodiazepines for a short-period of time has less intrinsic motivation to participate in the study.

In order to compare across the different types and dosages of benzodiazepines used in the sample, a conversion to a diazepam equivalent dose was used. Whilst this conversion is useful for research purposes, it is not without limitations. The conversion to diazepam equivalent dose is based on doses with comparable clinical effects, and it does not account for variation between preparations, such as time to onset and duration of effects. Furthermore, using a diazepam equivalent dose means that the unique effects of each individual preparation cannot be explored, and interesting findings may be obscured. Despite this, the use of diazepam equivalent doses is still a useful, and commonly utilised strategy for research examining the benzodiazepines. The alternative to this is would be to have a very large sample size, with enough occurrences of each drug type, to allow comparisons to be made between preparations.

One aspect that does not emerge from the current study is why the sample's benzodiazepine use has continued in such a chronic manner. There are a range of causative reasons that could contribute to this, such as; clinically justified use, poor clinical management, failed attempts at cessation, doctor-shopping, or illicit purchases. Similarly, it is not known what deprescribing interventions were typically received by these benzodiazepine users. What is established, is that there are significant barriers to reducing benzodiazepine use, such as the overwhelming withdrawal symptoms described by the sample in chapter 8. Furthermore, not all outcomes associated with benzodiazepine reduction are positive; for example, evidence suggests that a mild cognitive deficit may remain for people who have previously been chronic benzodiazepine users (Barker, Greenwood, Jackson, & Crowe, 2004). These factors may mean that incentive to reduce benzodiazepine use remains low. Future studies should take a longitudinal approach in order to understand the progression of long-term benzodiazepine users, including the

reasons for initial and ongoing use of benzodiazepines, and the clinical involvement and interventions with these patients. Longitudinal cross-over studies, including alternate pharmacological treatments, and psychological therapies should focus on the beneficial effects of ceasing benzodiazepine use.

Clinical Recommendations

There have been numerous quality guidelines released to direct the process of benzodiazepine prescription (for example: National Health and Medical Research Council, 1991; Royal Australian College of General Practitioners, 2015a, 2015b). When considering the issues regarding problematic benzodiazepine use that have been identified in this study, a review of current benzodiazepine guidelines revealed that in most instances there were already suggested procedures to circumvent these problems. What seems to be lacking is a regular application of these guidelines. In the Royal Australian College of General Practitioner's guidelines (2015b), much of the content focuses on achieving a more consistent approach to prescribing benzodiazepines.

It is proposed that one approach to standardising benzodiazepine prescription could be by replicating the opiate contracts that are typically used in the management of pain relief (Queensland Government Drug Dependence Unit, 2010). There have already been attempts to modify a contract for benzodiazepine use (for example: Royal Australian College of General Practitioners, 2015b), although they are not yet regularly used in practice. The aim of a benzodiazepine contract would be to instigate a discussion regarding the limitations of benzodiazepines, particularly the risks associated with ongoing use, and to consider alternate treatment approaches, such as cognitive-behavioural therapy.

Benzodiazepine contracts would guide the use of benzodiazepines and other therapies, through various stages of treatment. In order to reduce ongoing benzodiazepine use occurring without clear rationale, it is recommended that all benzodiazepine prescriptions should be accompanied by a benzodiazepine contract, that clearly documents agreed time frames and dates, for example when the

prescription will be reviewed or when alternative treatment is to commence. Benzodiazepine contracts would also improve communication between professionals, and could be used as a reference point for agreed upon principles (for example, a patient only obtaining prescriptions from one pharmacy). Importantly, benzodiazepine contracts would improve accountability for both patients and prescribers. They would provide a record that key benzodiazepine information has been discussed and agreed upon by both parties. Whilst prescriber autonomy and judgement will always be important, evidence from this study suggests that procedures surrounding benzodiazepine prescription need to be strengthened. Benzodiazepine contracts would ensure best practice standards are followed by individual prescribers, and the health profession as a whole.

Findings from the current qualitative study indicated many respondents felt that benzodiazepines were the most effective treatment to manage their symptoms quickly. Likewise, recent research found that GPs often prescribed benzodiazepines as they felt this was the best way to assist their patients, who often had overwhelming psychosocial problems (Anthierens, Habraken, Petrovic, & Christiaens, 2007). Contrary to these beliefs, benzodiazepines are rarely indicted as a first line treatment choice. Perhaps what is often lacking at both the prescriber, and patient level, is an awareness of the relative efficacy of psychological treatments, usually cognitive-behavioural therapy, in managing many of the conditions for which benzodiazepines are commonly prescribed. Treatment of various conditions should always be guided by best practice treatment protocols, such as those produced by the National Institute for Health and Care Excellence, or the British Association for Psychopharmacology. Undeniably, psychological treatments are more intensive in terms of time requirements for both patient and prescriber, and for them to be utilised as recommended, there must be clear referral pathways available, and medical practitioners must be encouraged to use these as a first treatment option. If a benzodiazepine script is initiated, then it is suggested that an accompanying benzodiazepine contract is used to outline a plan for complementary non-pharmacological treatments to occur.

Finally, it should be acknowledged that benzodiazepines, whilst frequently vilified, can also be a highly effective and safe medication when used correctly. There were some individuals in this cohort who reported they were able to use benzodiazepines occasionally when needed, to effectively manage symptoms, with minimal side-effects. The ongoing issue for prescribers is how to differentiate those who are receiving a positive effect, from the multitude of other problematic presentations. The use of a benzodiazepine contract as a standard measure, would reduce stigmatisation by ensuring everyone who receives a benzodiazepine prescription is treated equally.

Table 2 summarises the key recommendations for managing benzodiazepine use at each stage of treatment; these are proposed based on the review and findings of the current study. These recommendations are supported by other relevant guidelines.

Table 2. *Recommended Interventions during Benzodiazepine treatment, based on the findings of the current study and the extant literature.*

Stage of Treatment:	Suggested Interventions based on findings from the current study:	Supported by:		
		RACGP[1]	NICE[2]	BAP[3]
Patients requesting symptomatic relief	Comprehensive medical assessment	✓	✓	
	Relevant treatment protocol followed	✓	✓	✓
	Increased accessibility of Psychological services when indicated in treatment protocol	✓	✓	✓
New benzodiazepine script initiated	Benzodiazepine Contract initiated, including an exploration of Pros and Cons of use		✓	
	Benzodiazepine Contract initiated, including an agreement on a review date	✓		✓
Repeat benzodiazepine script requested	Risk/benefit analysis of benzodiazepine continuation reviewed	✓	✓	✓
	Standard policies for managing requests	✓		
Long-term benzodiazepine users	Review ongoing risks of use	✓	✓	
	Emphasise benefits of reduction in use	✓		
	Initiate benzodiazepine contract if not already documented	✓		
	Set date for cessation of use	✓		
	Initiate alternative treatment for underlying conditions	✓	✓	✓
Patient withdrawing from benzodiazepines	Gradual dose reduction	✓	✓	✓
	Psychological interventions used to manage withdrawal symptoms	✓		
	Provide psychological interventions with efficacy in treating underlying condition	✓	✓	✓
Collaboration with other health professionals	Real-time reporting systems			
	Limit number of prescribers and pharmacies involved per patient	✓		
	Communication between health professionals via benzodiazepine contract.	✓		

[1] Royal Australian College for General Practitioners (Royal Australian College of General Practitioners, 2015b) [2]National Institute for Health and Care Excellence (National Institute for Health and Care Excellence, 2014). [3]British Association for Pharmacology (Baldwin et al., 2013)

Conclusion

Benzodiazepines are a divisive medication. They are fast-acting, effective, and low cost, which means that they will likely remain a popular treatment choice. However, there are also significant risks involved with their use, including dependence, health and safety issues, and cognitive decline. Despite clinical guidelines first being published over 35 years ago, the current research shows that the use of benzodiazepines is often not concordant with these guidelines. In both the general and high risk population samples studied here, benzodiazepine use was chronic in duration and frequency. The most chronic user groups had an increased experience of safety incidents, and this association remained after controlling for a range of confounding variables. It is important that enough autonomy in benzodiazepine prescribing is retained to allow for the individual needs of patients. However, the use of benzodiazepines is at a point where accountability of prescription must be increased. Benzodiazepine contracts are proposed as a method to ensure consistency and best practice in prescribing occurs. The use of a contract would ensure prescribers and patients had an open conversation about the risks and benefits of benzodiazepine use. This is essential given that many of the current sample reported feeling ill-informed about benzodiazepines, and correspondingly their assessed knowledge about benzodiazepine side-effects was low. To maximise understanding and recall, key benzodiazepine information needs to be provided repeatedly, in a way that is attention-grabbing, easily understood, and accessible in a range of different formats. Many in this sample of chronic benzodiazepine users expressed a desire to reduce their use. This ambivalence about use is an opportunity to instigate change that should not be missed. However, to manage current chronic benzodiazepine users, and to counter more restrictive benzodiazepine prescribing, there needs to be an increased provision of more specialised services. These services would need to target the management of benzodiazepine dependence and withdrawal, and importantly provide alternative treatments and strategies to the use of benzodiazepines.

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APPENDIX

BENZODIAZEPINE USE, HEALTH, & DRIVING SURVEY

Benzodiazepines: Use, Accidents & Perceptions

Thank you for your interest in this research. This study is part of a research project conducted by Aneliese Poorter (DPsych student) and Dr Raimondo Bruno at the University of Tasmania. This study has been cleared in accordance with the ethical review processes of the University of Tasmania and complies with the guidelines of the National Statement on Ethical Conduct in Human Research. Your participation is completely voluntary.

What is the purpose of this study?

The purpose of this study is to investigate the experience of people who take benzodiazepines (sleeping pills, tranquilisers). In particular, the study will look at driving practices, experiences of accidents and injuries, memory failures and personal perspectives regarding benzodiazepines.

What will I be asked to do?

Taking part in this study involves completing an online survey and should take about 25 minutes, or slightly more or less depending on your experience with these medications. Questions ask about medication use, driving practices, recent accidents, and injuries you may have experienced, times when you have forgotten to do something and your own perceptions of the impact of benzodiazepines on your safety.

What are the benefits of participating in this study?

Your participation will also assist us to better understand the role of benzodiazepines in road safety. This information is of high importance to health professionals and policy makers, and will provide useful information to prescribers of these medications. Upon completion you may choose to be entered into a prize draw to win one of three $500 Coles-Myer gift vouchers.

Are there any risks associated with participating in this study?

This study involves no more than minimal risk to you, i.e., the level of risk encountered in daily life. No deception is involved in this study. However, should you become uncomfortable or upset whilst completing the survey, please stop the survey and seek assistance from Lifeline, on 13 11 14, which operates 24 hours a day, 7 days a week (within Australia). If you do not reside in Australia, you may find your local service provider on the International White and Yellow Pages, www.wayp.com. If you have any questions or concerns about your

benzodiazepine use as a result of completing this survey, you should discuss these with your regular doctor.

It is also important for you to know that all questions are optional. Please skip any questions in this survey that you feel uncomfortable about answering.

How will my confidentiality and privacy be maintained?

Our server uses a 128bit encryption which is backed by Verisign, the world's largest security certificate provider. This is the same level of encryption used by banks and the Australian Tax Office. Therefore, the responses you provide will remain completely anonymous and confidential, as the risk of identification is negligible.

However, you may also choose to use an anonymizer, which will mask your IP address. This will mean that both the computer you are using as well as the responses you provide will be completely unidentifiable. Anonymizers work by inserting a fake computer in between your computer and our server, hence masking your IP address. For more information, see: http://www.torproject.org/ & http://www.thefreecountry.com/security/anonymous.shtml

How do I participate?

Below you will find a short list of statements that you will be asked to agree to in order to indicate your willingness to participate in this survey. There are also some brief questions determining your eligibility for this study. After answering these questions you will be directed to the start of the survey. If you do not wish to participate, we thank you for your time - you can close this browser window to end this session. If you wish to discontinue your participation at any point during the study, you may do so by closing your internet browser.

Concerns and complaints

If you have any questions about this study, please contact Aneliese Poorter (apoorter@utas.edu.au) or Dr Raimondo Bruno at (Raimondo.Bruno@utas.edu.au)

This study has been approved by the Tasmanian Social Science Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on 03 6226 7479 or human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote Ethics Reference Number H0012343.

Please read the following statements:

- ☐ I have read and understood the above information relating to this study.
- ☐ I understand the nature and possible effects of this study.
- ☐ I understand that this study involves answering questions about my benzodiazepine use, experiences of driving-related and other accidents and perceptions regarding benzodiazepines.
- ☐ I understand that all questions are optional and that I may choose to not answer any questions that I am uncomfortable with.
- ☐ I understand that all research data will be securely stored on a password protected server at the University of Tasmania.
- ☐ I understand that my participation is voluntary and that I cannot be identified in any way.

Respondents that did not agree with the above statements could not access the remainder of the survey

INFORMATION ABOUT YOU

These first few questions ask some basic information about you. Remember this information will not be used to identify anyone, it simply helps us to create a picture of the people completing this survey.

To help us determine that you are eligible to participate in this study, please indicate whether you agree with the following statements:

Please choose the appropriate response for each item:

	I agree	I disagree
I am at least 18 years of age	☐	☐
I have taken a benzodiazepine in the past 12 months	☐	☐

Respondents that did not tick 'I agree' to both statements could not access the remainder of the survey

What is your gender?

Please choose **all** that apply:

- ☐ *Female*
- ☐ *Male*
- ☐ *Transgender*

How old are you?

Please answer age in years. Please write your answer here:

[ ]

What is your current residential postcode?

Please write your answer here:

[ ]

What is your current marital status?

Please choose **only one** of the following:

- ☐ *Never married*
- ☐ *Married/Defacto*
- ☐ *Widowed*
- ☐ *Divorced*
- ☐ *Separated but not divorced*

How would you best describe your household?

Please choose **only one** of the following:

- ☐ *Single person household*
- ☐ *Single parent household*
- ☐ *You and spouse/partner with no children*
- ☐ *You and spouse/partner with one or more children at home*
- ☐ *Shared household*
- ☐ *Living with parents*

What is the highest level of school that you have completed?

Please choose **only one** of the following:

- ☐ Still at secondary school
- ☐ Did not go to school
- ☐ Year 8 or below
- ☐ Year 9 or equivalent
- ☐ Year 10 or equivalent
- ☐ Completed HSC/HEC (Year 12 or equivalent)

Have you completed any further qualifications?

Please choose **only one** of the following:

- ☐ No
- ☐ No, still studying for first qualification
- ☐ Yes

What qualification/s are you currently studying for?

Please choose **all** that apply:

- ☐ Trade Certificate
- ☐ Other Certificate (e.g. TAFE, Cert III etc.)
- ☐ Associate or Undergraduate Diploma
- ☐ Bachelor's Degree
- ☐ Graduate Diploma/Certificate
- ☐ Postgraduate Degree
- ☐ Other:

What is the highest level of further education you have reached so far?

Please choose **only one** of the following:

- ☐ Trade Certificate
- ☐ Other Certificate (e.g. TAFE, Cert III)
- ☐ Associate or Undergraduate Diploma
- ☐ Bachelor's Degree
- ☐ Graduate Diploma/Certificate
- ☐ Postgraduate Degree
- ☐ Other

How would you best describe your current employment situation?

Please choose **all** that apply:

- ☐ Not Employed
- ☐ Retired/Pensioner
- ☐ Home Duties
- ☐ Part time/Casual Work (less than 20 hours/week)
- ☐ Full time work
- ☐ Other:

What is the total of all wages/salaries, government benefits, allowances and other income that you usually receive per week or per year (before tax and other deductions)?

Please choose **only one** of the following:

- $1-$149 /week ($1-$7,799 / year)
- $150-$249 / week ($7,800-$12,999 / year)
- $250-$399 / week ($13, 000-$20,799 / year)
- $400-$599 / week ($20,800-$31, 199 / year)
- $600-$799 / week ($31,200-$41,599 / year)
- $800-$999 / week ($41,600-$51,999 / year)
- $1,000-$1,299 / week ($52,000-$67,599 / year)
- $1,300-$1,599 / week ($67,600-$83,199 / year)
- $1,600-$1,999 / week ($83,200-$103,999 / year)
- $2,000 or more / week ($104,000 or more / year)
- Nil income
- Negative income

Have you ever driven a motor vehicle?

Please choose **only one** of the following:

- No
- Yes

KEY MEDICATION INFORMATION

To help us customise this survey to you, please answer the following key questions about your medication use.

What best describes your reasons for use of benzodiazepines?

Please choose **all** that apply:

- ☐ I'm taking them to help with my sleep
- ☐ I'm taking them to help with my anxiety
- ☐ I'm taking them to help with my pain
- ☐ I'm taking them for some other reason

Which of the following best describes your pattern of taking benzodiazepines?

Please choose **all** that apply:

- ☐ I've been taking them daily or almost daily, for less than a month
- ☐ I've been taking them daily or almost daily, for more than a month
- ☐ I've been taking them daily or almost daily, for a year or more
- ☐ I've been taking them every now and then, for less than a month
- ☐ I've been taking them every now and then, for more than a month
- ☐ I've been taking them every now and then, for a year or more

In the last year have you taken any of the following types of prescription medications (this includes prescription medications that may not have been prescribed for you)?

Please choose **all** that apply:

- ☐ Antidepressant or mood lifting medications (e.g. Zoloft, Prozac, Lovan)
- ☐ Prescription pain killers or Opioids (e.g. Panadeine Forte, Oxycontin, Tramal)
- ☐ Strong tranquilizers or Antipsychotics (e.g. Seroquel, Risperdal)
- ☐ None of these

The above question was used to determine which medications were examined in more detail later in the survey.

YOUR MEDICATION USE: BENZODIAZEPINES

Please help us to get an idea of your benzodiazepine use by answering the following questions about when and how often you take them.

In the past 12 months have you used any of the following benzodiazepines?

Please choose the appropriate response for each item:

The first names listed here are active ingredients in the medication. You may also know these medications by their brand name, some common brand names are listed in brackets.

	No	Yes
Alprazolam (Alprax, Kalma, Ralozam, Xanax)	☐	☐
Bromazepam (Lexotan)	☐	☐
Clobazam (Frisium)	☐	☐
Diazepam (Antenex, Valium, Valpam)	☐	☐
Flunitrazepam (Hypnodorm)	☐	☐
Lorazepam (Ativan)	☐	☐
Nitrazepam (Alodorm, Mogadon)	☐	☐
Oxazepam (Alepam, Murelax, Serepax)	☐	☐
Temazepam (Normison, Temaze, Temtabs)	☐	☐

1. Which best describes your use of alprazolam:

Please choose **only one** of the following:

- ☐ I take it every day
- ☐ I take it for a brief period then stop
- ☐ I only take it when I need it

For each of the active ingredients listed above that were answered 'YES', the following questions (1-8) were then asked (alprazolam provided as an example)

2. Which of the following best describes your use of alprazolam:

Please choose **only one** of the following:

- ☐ I'm taking it exactly as prescribed
- ☐ I'm taking less than was prescribed
- ☐ I'm taking more than was prescribed
- ☐ I'm not prescribed this medication

3. When do you typically take alprazolam:

Please choose **all** that apply:

- ☐ In the morning
- ☐ In the afternoon
- ☐ In the night

4. In the last month how many days did you take alprazolam?

Please write your answer here:

If you took it every day please put *'30'*. If you did not take it at all, please put *'0'*.

5. When you've taken alprazolam what has been your usual dose per day?

Please write your answer here:

If possible please record the total milligrams that you would usually take in one day.

If you're unsure about how many milligrams you take, just type in the number of tablets you have each day and describe the tablet.

6. Approximately what date did you start taking alprazolam?

Please enter a date:

If you are unsure of the exact date you started, please put the first of the month. E.g. If you think you started in July 2012, select 1.7.2012.

7. Approximately when did you finish taking alprazolam?

Please enter a date:

If you are unsure of the exact date you finished, please put the last day of the month. E.g. If you think you finished in July 2012, select 31.7.2012.

If you are still taking this medication, please enter today's date.

8. Did you take alprazolam yesterday?

Please choose only one of the following:

- ☐ Yes
- ☐ No

Following are some questions about how important benzodiazepines are in your life

Please select the most accurate answer for the statements below:

	Not difficult	Quite difficult	Very difficult	Impossible
How difficult would you find it to stop or go without your benzodiazepines?	☐	☐	☐	☐
	Never/almost never	**Sometimes**	**Often**	**Always/ Nearly always**
Have you wished you could stop taking benzodiazepines?	☐	☐	☐	☐
Have you worried about your use of benzodiazepines?	☐	☐	☐	☐
Has the prospect of missing a dose made you anxious or worried	☐	☐	☐	☐
Have you ever thought your use of benzodiazepines was out of control?	☐	☐	☐	☐

CURRENT LICENCE AND DRIVING

We're interested in your experience on the road, so these next few questions are about your driving history.

What licence or licences do you currently hold?

Please choose **all** that apply:

- ☐ Car: Learner's permit
- ☐ Car: Provisional licence/P plates
- ☐ Car: Full driver's licence
- ☐ Car: Restricted licence
- ☐ Heavy vehicle licence
- ☐ Bus Driver's licence
- ☐ Motorcycle: Learner's permit
- ☐ Motorcycle: Provisional licence
- ☐ Motorcycle: Full licence
- ☐ Taxi or hire care licence
- ☐ None

How long have you had your longest driver's licence or permit?

Please choose **only one** of the following:

- ☐ Less than 6 months
- ☐ Less than 1 year
- ☐ 1 to 2 years
- ☐ 2 to 3 years
- ☐ 3 to 5 years
- ☐ 6 to 10 years
- ☐ Over 10 years

How often do you drive a vehicle on the road, assuming an average week?

Please choose **only one** of the following:

- ☐ Less than once a week
- ☐ At least one day a week
- ☐ 2 to 3 days a week
- ☐ 4 to 6 days a week
- ☐ Every day of the week

How far (kilometres) do you drive per week on average?

Please write your answer here:

How many hours would you personally drive a vehicle on the road each week?

Please write your answer here:

What percentage of your driving would be on roads with a speed limit of 80km/hour or more?

Please choose **only one** of the following:

- ☐ Less than 20%
- ☐ 20 to 50%
- ☐ 50%
- ☐ 51 to 80%
- ☐ More than 80%

ROAD ACCIDENTS

The following section includes questions about traffic accidents that you may have been involved in.

If you find this distressing remember that you may exit this survey at any time. Please contact lifeline on 13 11 14 if you feel like you want to talk to someone.

In the last 12 months when you have been driving, how many close calls have you had (i.e. incidents that almost resulted in a crash but did not)?

Please write your answer here:

For how many of these 'close calls' do you think you were taking a benzodiazepine in the same time period?

Please write your answer here:

When you have been driving, how many road crashes have you ever been involved in?

Please choose **only one** of the following:

- ☐ None
- ☐ One
- ☐ 2-3
- ☐ 4-5
- ☐ 5-10
- ☐ More than 10

'Road Crash' includes any incident in which you were driving and which yourself or another person were injured *or* where there was damage to property or vehicles.

In the last 12 months when you have been driving, how many road crashes have you had?

Please write your answer here:

'Road Crash' includes any incident in which you were driving and which yourself or another person were injured *or* where there was damage to property or vehicles.

For how many of these accidents do you think you were taking a benzodiazepine in the same time period?

Please write your answer here:

Think of the most serious crash that you have had in the last 12 months, when you have been driving, and answer the following questions (questions a-h).

a. Were you at fault for this crash?

Please choose **only one** of the following:

- ☐ Yes
- ☐ No

b. Were you taking a benzodiazepine at the time of this accident?

Please choose **only one** of the following:

- ☐ Yes
- ☐ No

c. How many hours before the accident do you think you would have had a benzodiazepine?

Please write your answer here:

d. Was there another vehicle involved in this crash?

Please choose only one of the following:

- ☐ Yes
- ☐ No

e. What vehicle were you driving?

Please choose **only one** of the following:

- ☐ Car
- ☐ Utility
- ☐ 4WD
- ☐ Light Truck
- ☐ Heavy vehicle
- ☐ Motorcycle
- ☐ Other

f. What was the result of this crash?

Mark the most serious result:

- ☐ There was minor damage to a vehicle but no one was injured
- ☐ There was major damage to a vehicle but no one was injured
- ☐ Someone was injured but did not need to be hospitalised
- ☐ Someone died or needed to be hospitalised
- ☐ None of the above
- ☐ Don't know

g. Where were you driving?

Please choose **only one** of the following:

- ☐ In a capital city
- ☐ In a regional city/large town
- ☐ In the country on a country road
- ☐ In the country on highway/freeway
- ☐ Off road (including rural use)
- ☐ Don't know/can't recall

h. What speed zone were you driving in?

Please choose **only one** of the following:

- 40km/hour
- 50km/hour
- 60km/hour
- 70km/hour
- 80km/hour
- 100km/hour
- 110km/hour
- Don't know/can't recall

How many times have you lost your licence due to traffic offences?

Please choose **only one** of the following:

- Never
- Once
- Twice
- Three times
- Four or more times

How many licence demerit points have you lost in the last 12 months?

Please choose **only one** of the following:

- None
- One
- Two
- Three
- 4-6
- 7-9
- 10-12

YOUR PERCEPTIONS OF BENZODIAZEPINES

These next questions are asking for your personal opinions on how you think benzodiazepines might affect you.

Tick all of the symptoms listed below that you think could be a side-effect of taking benzodiazepines:

Please choose **all** that apply:

- ☐ Nausea
- ☐ Drowsiness
- ☐ Sedation
- ☐ Light-headedness
- ☐ Double vision
- ☐ Slurred Speech
- ☐ Indigestion
- ☐ Memory Loss
- ☐ Ataxia (difficulty with coordination)
- ☐ Constipation

Please answer this question using your own knowledge only

When you first started using benzodiazepines, how did you learn about the possible negative side effects?

Please choose **all** that apply:

- ☐ I wasn't aware of the side effects
- ☐ The Doctor told me
- ☐ The Pharmacist told me
- ☐ I read the information in the box
- ☐ I saw a warning label on the box
- ☐ A friend/family member told me
- ☐ The Internet
- ☐ Other:

For each of the following questions about symptomology, if a respondent indicated that they had experienced the symptom, then the follow up question asking about change in the symptom was presented

Have you ever experienced any daytime drowsiness that you feel is related to your benzodiazepine use (e.g. feeling sluggish or difficulty getting going in the morning)?

Please choose **only one** of the following:

- ☐ Yes
- ☐ No

Since you began taking benzodiazepines, has this daytime drowsiness:

Please choose **only one** of the following:

- ☐ Stayed the same
- ☐ Worsened
- ☐ Improved

Have you ever experienced any poor concentration that you feel is related to your benzodiazepine use?

Please choose **only one** of the following:

- ☐ Yes
- ☐ No

Since you began taking benzodiazepines, has this poor concentration:

Please choose **only one** of the following:

- ☐ Stayed the same
- ☐ Worsened
- ☐ Improved

Have you ever experienced any light-headedness that you feel is related to your benzodiazepine use?

Please choose **only one** of the following:

- ☐ Yes
- ☐ No

Since you began taking benzodiazepines, has this light-headedness:

Please choose **only one** of the following:

- ☐ Stayed the same
- ☐ Worsened
- ☐ Improved

Have you ever experienced any memory loss that you feel is related to your benzodiazepine use?

Please choose **only one** of the following:

- ☐ Yes
- ☐ No

Since you began taking benzodiazepines, has this memory loss:

Please choose **only one** of the following:

- ☐ Stayed the same
- ☐ Worsened
- ☐ Improved

Have you ever experienced any slurred speech that you feel is related to your benzodiazepine use?

Please choose **only one** of the following:

- ☐ Yes
- ☐ No

Since you began taking benzodiazepines, has this slurred speech:

Please choose **only one** of the following:

- ☐ Stayed the same
- ☐ Worsened
- ☐ Improved

Have you ever experienced any confusion that you feel is related to your benzodiazepine use?

Please choose **only one** of the following:

- ☐ Yes
- ☐ No

Since you began taking benzodiazepines, has this confusion:

Please choose **only one** of the following:

- ☐ Stayed the same
- ☐ Worsened
- ☐ Improved

When you first started taking benzodiazepines (e.g. for the first month), how did you think they impacted on your driving ability?

Please choose **only one** of the following:

- ☐ No effect
- ☐ Worsened
- ☐ Improved
- ☐ Not applicable

If you selected *improved* or *worsened,* please specify briefly how your driving ability was impacted.

How do you think your use of benzodiazepines currently impacts on your driving ability?

Please choose **only one** of the following:

- ☐ No effect
- ☐ Worsens
- ☐ Improves
- ☐ Not applicable

If you selected *improves* or *worsens,* please specify briefly how your driving ability was impacted.

Whilst taking benzodiazepines have you taken any safety precautions in regards to driving?

Please choose **all** that apply:

- ☐ I did not take any precautions
- ☐ I did not drive at all
- ☐ I did not drive immediately after I had taken a benzodiazepine
- ☐ I drove more slowly
- ☐ I stopped taking benzodiazepines
- ☐ I took other things to counter any side-effects
- ☐ Other:

Do you worry about using benzodiazepines?

Please choose **only one** of the following:

- ☐ No
- ☐ Yes

If you answered yes, please explain briefly

Do you feel that taking benzodiazepines has negatively impacted on your safety in any other way? Please explain briefly:

Please write your answer here:

OTHER ACCIDENTS, BUMPS & BRUISES

Another area that we are interested in is your experience of non-road related accidents (for licenced driver's road accidents are covered in an earlier section). These questions ask about any major injuries as well as more minor 'bumps and bruises'.

Remember if you find this distressing, you can exit the survey at any time. Please contact Lifeline on 13 11 14 if you feel like you want to talk to someone.

Thinking about the last 12 months, how many accidents have you had that required medical attention from someone else (e.g. a first aider, GP, nurse, or hospital doctor)?

Please write your answer here:

Thinking about your most recent accident that required medical attention, how were you injured?

Please choose **all** that apply:

- ☐ Being in contact with moving machinery
- ☐ Being struck by a moving object
- ☐ Being struck by a moving vehicle
- ☐ Striking something stationary
- ☐ Being injured whilst handling, lifting or carrying
- ☐ A slip, trip or fall on the same level
- ☐ A fall from a height
- ☐ Being trapped by something collapsing or overturning
- ☐ Drowning or asphyxiation
- ☐ Exposure to a harmful substance
- ☐ Exposure to a fire
- ☐ Exposure to an explosion
- ☐ Being in contact with electricity
- ☐ Being injured by an animal
- ☐ An act of violence
- ☐ Being injured whilst playing sport
- ☐ Other:

Where were you injured?

Please choose **all** that apply:

- ☐ Face
- ☐ Head
- ☐ Neck
- ☐ Hand
- ☐ Arm
- ☐ Torso
- ☐ Back
- ☐ Leg
- ☐ Foot
- ☐ Other:

What sort of injury or injuries did you sustain?

Please choose **all** that apply:

- ☐ Amputation
- ☐ Fracture/broken bone
- ☐ Dislocation
- ☐ Concussion
- ☐ Internal injuries
- ☐ Lacerations (open cuts or wounds)
- ☐ Bruising
- ☐ Burns
- ☐ Poisoning or gassing
- ☐ Sprain or strain
- ☐ Injuries caused through contact with electricity
- ☐ Injuries requiring resuscitation

What medical attention did you require?

Please choose **all** that apply:

- ☐ Treated by a G.P.
- ☐ Treated by a nurse at the G.P. surgery
- ☐ Attended Accident & Emergency
- ☐ Admitted to hospital for LESS than 24 hours
- ☐ Admitted to hospital for MORE than 24 hours
- ☐ Other:

In the last 12 months how frequently have you had minor injuries (e.g. cuts and bruises) that did not require medical attention from anyone else?

Please choose **only one** of the following:

- ☐ Not at all
- ☐ Rarely
- ☐ Occasionally
- ☐ Quite frequently
- ☐ Very frequently

In the last month how frequently have you had minor injuries (e.g. cuts and bruises) that did not require medical attention from anyone else?

Please choose **only one** of the following:

- ☐ Not at all
- ☐ Rarely
- ☐ Occasionally
- ☐ Quite frequently
- ☐ Very frequently

Approximately how many times have you visited your G.P. in the last 12 months?

Please write your answer here:

Approximately how many times have you visited hospital as an outpatient in the last 12 months?

Please write your answer here:

Approximately how many times have you visited hospital as an inpatient in the last 12 months?

Please write your answer here:

YOUR MEMORY IN EVERYDAY SITUATIONS

This questionnaire looks at the type of memory mistakes that people make in normal everyday life. We would like you to tell us how often these kind of things happen to you.

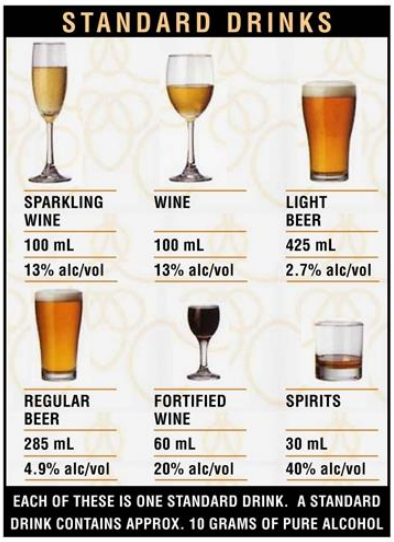
Please choose the appropriate response for each item:	Never	Rarely	Sometimes	Quite often	Very often
Do you decide to do something in a few minutes time and then forget to do it?	□	□	□	□	□
Do you fail to recognise a place that you have visited before?	□	□	□	□	□
Do you fail to do something you were supposed to do a few minutes later even though it's there in front of you, like take a pill or turn off the kettle?	□	□	□	□	□
Do you forget to do something that you were told a few minutes before?	□	□	□	□	□
Do you forget appointments if you are not prompted by someone else or by a reminder such as a calendar or diary?	□	□	□	□	□
Do you fail to recognise a character in a radio or television show from scene to scene?	□	□	□	□	□
Do you forget to buy something you planned to buy, like a birthday card, even when you see the shop?	□	□	□	□	□
Do you fail to recall things that have happened to you in the last few days?	□	□	□	□	□
Do you repeat the same story to the same person on different occasions?	□	□	□	□	□
Do you intend to take something with you, before leaving a room or going out, but minutes later leave it behind, even though it's there in front of you?	□	□	□	□	□
Do you mislay something that you have just put down, like a magazine or glasses?	□	□	□	□	□
Do you fail to mention or give something to a visitor that you were asked to pass on?	□	□	□	□	□
Do you look at something without realising you have seen it moments before?	□	□	□	□	□
If you tried to contact a friend or relative who was out, would you forget to try again later?	□	□	□	□	□
Do you forget what you watched on television the previous day?	□	□	□	□	□
Do you forget to tell someone something you had meant to mention a few minutes ago?	□	□	□	□	□

ALCOHOL USE

Because Alcohol use can affect health and interfere with some medications, it is important we ask you some questions about your use of alcohol. Your answers will remain confidential so please answer as accurately as possible.

Try to answer the questions in terms of 'standard drinks'. See the image below for common standard drink portions.

Each of the following contains ONE standard drink:



How often do you have a drink containing alcohol?

Please choose **only one** of the following:

- ☐ Never
- ☐ Monthly or less
- ☐ 2-4 times per month
- ☐ 2-3 times per week
- ☐ 4 or more times a week

How many drinks containing alcohol do you have on a typical day when you are drinking?

Please choose **only one** of the following:

- ☐ 1 or 2
- ☐ 3 or 4
- ☐ 5 or 6
- ☐ 7 to 9
- ☐ 10 or more

How often do you have six or more drinks on one occasion?

Please choose **only one** of the following:

- Never
- Less than monthly
- Monthly
- Weekly
- Daily or almost daily

In the past 12 months how likely is it that you have driven when over the blood alcohol limit (the limit that applies to your licence at the time)?

Please choose **only one** of the following:

- Definitely not
- Very unlikely
- Fairly unlikely
- Fairly likely
- Very likely

OTHER DRUG USE AND DRIVING

Because there are various drugs that can influence your driving ability, we are interested to know whether you have consumed certain drugs before driving. These next questions ask about some legal and illicit drugs.

How often have you used cannabis in the past 12 months?

Please choose **only one** of the following:

- Never
- Less than monthly
- Monthly
- Fortnightly
- Weekly
- More than once a week
- Daily

In the past 12 months how likely is it that you have driven when under the influence of cannabis?

Please choose **only one** of the following:

- Definitely not
- Very unlikely
- Fairly unlikely
- Fairly likely
- Very likely

How often have you used other illicit (illegal) drugs (e.g. speed, ecstasy, opioids) in the past 12 months?

Please choose **only one** of the following:

- Never
- Less than monthly
- Monthly
- Fortnightly
- Weekly
- More than once a week
- Daily

In the past 12 months how likely is it that you have driven when under the influence of other illicit drugs (e.g. speed, ecstasy)?

Please choose **only one** of the following:

- Definitely not
- Very unlikely
- Fairly unlikely
- Fairly likely
- Very likely

How often have you used non-prescription codeine-based painkillers (e.g. Mersyndol, Panadeine, Chemists Own Strong Pain Relief) in the past 12 months?

Please choose **only one** of the following:

- Never
- Less than monthly
- Monthly
- Fortnightly
- Weekly
- More than once a week
- Daily

In the past 12 months how likely is it that you have driven when under the influence of other non-prescription codeine based painkillers?

Please choose **only one** of the following:

- Definitely not
- Very unlikely
- Fairly unlikely
- Fairly likely
- Very likely

How often have you used prescription painkillers (e.g. morphine, oxycodone) in the past 12 months?

Please choose **only one** of the following:

- Never
- Less than monthly
- Monthly
- Fortnightly
- Weekly
- More than once a week
- Daily

In the past 12 months how likely is it that you have driven when under the influence of prescription painkillers (e.g. morphine, oxycodone)?

Please choose **only one** of the following:

- Definitely not
- Very unlikely
- Fairly unlikely
- Fairly likely
- Very likely

In the past 12 months how likely is it that you have driven when under the influence of prescription sleeping tablets or anti-anxiety medications (e.g. diazepam, temazepam, oxazepam)?

Please choose **only one** of the following:

- Definitely not
- Very unlikely
- Fairly unlikely
- Fairly likely
- Very likely

YOUR HEALTH

In general how would you say your health is?

Please choose **only one** of the following:

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

The following questions are about activities you might do during a typical day. How much does your health limit you in these activities?

Please choose the appropriate response for each item:

	Limited a lot	Limited a little	Not limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Please choose the appropriate response for each item:

	No	Yes
Accomplished less than you would like	☐	☐
Were limited in the kind of work or other activities	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Please choose the appropriate response for each item:

	No	Yes
Accomplished less than you would like	☐	☐
Did work or other activities less carefully than usual	☐	☐

During the past 4 weeks how much did pain interfere with your normal work (including both work outside the home and housework)?

Please choose **only one** of the following:

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely
- ☐ Very severe

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question please provide the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks:

Please choose the appropriate response for each item:

	All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.)?

Please choose **only one** of the following:

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little bit of the time
- ☐ None of the time

In the last 12 months has a health professional told you that you have any of the following:

Please choose the appropriate response for each item:

	Yes	No
Chronic ongoing problems with pain	☐	☐
Sleep Apnoea	☐	☐
A neurological condition (such as Epilepsy or a Stroke)	☐	☐
Chronic Lung Disease (like COPD or Emphysema)	☐	☐
Depression	☐	☐
Anxiety	☐	☐
Dependence on a substance (like alcohol or other drugs)	☐	☐
Some other mental health condition	☐	☐
Any other chronic ongoing condition	☐	☐

These questions ask about your mood over the last 4 weeks.

For all questions please select the most appropriate response. In the last 4 weeks:	None of the time	A little of the time	Some of the time	Most of the time	All of the time
About how often did you feel tired out for no good reason?	☐	☐	☐	☐	☐
About how often did you feel nervous?	☐	☐	☐	☐	☐
About how often did you feel so nervous that nothing could calm you down?	☐	☐	☐	☐	☐
About how often did you feel hopeless?	☐	☐	☐	☐	☐
About how often did you feel restless or fidgety?	☐	☐	☐	☐	☐
About how often did you feel so restless that you could not sit still?	☐	☐	☐	☐	☐
About how often did you feel depressed?	☐	☐	☐	☐	☐
About how often did you feel that everything was an effort?	☐	☐	☐	☐	☐
About how often did you feel so sad that nothing could cheer you up?	☐	☐	☐	☐	☐
About how often did you feel worthless?	☐	☐	☐	☐	☐

YOUR MEDICATION USE: ANTIDEPRESSANT OR MOOD-LIFTING MEDICATIONS

In this section we ask about any antidepressant medications that you may be taking. Whilst the focus of this study is on benzodiazepines, it is important we know about antidepressants so we can account for any effect they might have on your health and well-being.

In the past 12 months have you used any of the following antidepressant medications?

Please choose the appropriate response for each item:

	No	Yes
Amitriptyline (Endep)	☐	☐
Agomelatine (Valdoxan)	☐	☐
Citalopram (Celapram, Celica, Ciazil, Cipramil, Citalo)	☐	☐
Clomipramine (Anafranil, Placil)	☐	☐
Desvenlafaxine (Pristiq)	☐	☐
Dothiepin (Dothep)	☐	☐
Doxepin (Deptran, Sinequan)	☐	☐
Duloxetine (Cymbalta)	☐	☐
Escitalopram (Escicor, Esipram, Esitalo, Lexam, Lexapro)	☐	☐
Fluoxetine (Auscap, Fluohexal, Lovan, Prozac, Zactin)	☐	☐
Fluvoxamine (Faverin, Luvoz, Movox, Voxam)	☐	☐
Imipramine (Tofranil, Tolerade)	☐	☐
Mianserin (Lumin, Tolvon)	☐	☐
Mirtazepine (Avanza, Axit, Mirtazon)	☐	☐
Moclobemide (Amira, Aurorix, Clobemix)	☐	☐
Nortriptyline (Allegron)	☐	☐
Paroxetine (Aropax, Extine, Paxtine)	☐	☐
Phenelzine (Nardil)	☐	☐
Sertraline (Concorz, Eleva, Sertra, Setrona, Xydep, Zoloft)	☐	☐
Tranylcypromine (Parnate)	☐	☐
Trimipramine (Surmontil)	☐	☐
Reboxetine (Edronax)	☐	☐
Venlafaxine (Efexor-XR)	☐	☐

The first names listed here are active ingredients in the medication. You may also know these medications by their brand name, some common brand names are listed in brackets.

YOUR MEDICATION USE: STRONG TRANQUILISERS OR ANTI-PSYCHOTICS

This section asks about strong tranquilisers, such as quetiapine and risperidone, and how you may have used them. Whilst the focus of this study is on benzodiazepines, it is important we know about tranquilising medications so we can account for any effect they might have on your health and well-being.

In the past 12 months have you used any of the following strong tranquilisers (such as quetiapine, risperidone)?

Please choose the appropriate response for each item:

	No	Yes
Amisulpride (Amipride, Solian, Sulpriz)	☐	☐
Aripiprazole (Abilify)	☐	☐
Asenapine (Saphris)	☐	☐
Chlorpromazine (Largactil)	☐	☐
Clozapine (Clopine, Clozaril)	☐	☐
Droperidol (Droleptan)	☐	☐
Flupenthixol (Fluanxol)	☐	☐
Fluphenazine (Modecate)	☐	☐
Haloperidol (Serenace)	☐	☐
Olanzapine (Zyprexa)	☐	☐
Paliperidone (Invega, Invega Sustenna)	☐	☐
Pericyazine (Neulactil)	☐	☐
Quetiapine (Seroquel, Seroquel XR)	☐	☐
Risperidone (Resdone, Resperdal, Rispa, Rixadone, Ozidal)	☐	☐
Sertindole (Serdolect)	☐	☐
Trifluperazine (Stelazine)	☐	☐
Ziprasidone (Zeldox)	☐	☐
Zuclopethixol (Clopixol)	☐	☐

The first names listed here are active ingredients in the medication. You may also know these medications by their brand name, some common brand names are listed in brackets.

YOUR MEDICATION USE: PRESCRIPTION PAIN-KILLERS OR OPIOID MEDICATIONS

In this section we ask about any opioid medications that you may be taking. Whilst the focus of this study is on benzodiazepines, it is important we know about painkillers so we can account for any effect they might have on your health and well-being.

In the past 12 months have you used any of the following opioid medications?

Please choose the appropriate response for each item:

	No	Yes
Buprenorphine (Subutex, Suboxone, Norspan)	☐	☐
Prescription-only Codeine (Panadeine Forte, Codalgin, Prodeine Forte)	☐	☐
Fentanyl (Durogesic, Denpax, Actiq)	☐	☐
Hydromorphone (Dilaudid, Jurnista)	☐	☐
Methadone (Physeptone)	☐	☐
Morphine (MS Contin, Momex, Ordine)	☐	☐
Oxycodone (Oxycontin, Endone)	☐	☐
Pethidine	☐	☐
Tramadol (Tramal, Zydol, Durotram)	☐	☐

The first names listed here are active ingredients in the medication. You may also know these medications by their brand name, some common brand names are listed in brackets.

YOUR MEDICATION USE: OTHER MEDICATIONS

In this section we ask about some selected other medications that you may be taking. Whilst the focus of this study is on benzodiazepines, it is important we know about these other medications so we can account for any effect they might have on your health and well-being.

In the past 12 months have you used any of the following other medications?

Please choose the appropriate response for each item:

	No	Yes
Acamprosate (Campral)	☐	☐
Buspirone (Buspar)	☐	☐
Buproprion (Prexaton, Zyban SR)	☐	☐
Clonidine (Catapres)	☐	☐
Doxylamine (Dozile, Restavit)	☐	☐
Disulfiram (Antabuse)	☐	☐
Lithium (Lithicarb, Quilonum SR)	☐	☐
Melatonin (Circadin)	☐	☐
Naltrexone (ReVia)	☐	☐
Varenicline (Champix)	☐	☐
Zolpiclone (Imovane, Imrest)	☐	☐
Zolpidem (Dormizol, Somidem, Stildem, Stilnox, Zolpibell)	☐	☐

The first names listed here are active ingredients in the medication. You may also know these medications by their brand name, some common brand names are listed in brackets.

For each of the above sections on anti-depressants, strong tranquillisers, and pain killers, the active ingredients that were answered 'YES', were then followed with next 5 questions

1. Which best describes your use of amitriptyline:

Please choose **only one** of the following:

- ☐ I take it every day
- ☐ I take it for a brief period then stop
- ☐ I only take it when I need it

2. Which of the following best describes your use of amitriptyline:

Please choose **only one** of the following:

- ☐ I'm taking it exactly as prescribed
- ☐ I'm taking less than was prescribed
- ☐ I'm taking more than was prescribed
- ☐ I'm not prescribed this medication

3. In the last month how many days did you take amitriptyline?

Please write your answer here:

If you took it every day please put *'30'*

If you did not take it at all, please put *'0'*.

4. When you've taken amitriptyline what has been your usual dose per day?

Please write your answer here:

If possible please record the total milligrams that you would usually take in one day.

If you're unsure about how many milligrams you take, just type in the number of tablets you have each day and describe the tablet.

5. Did you take amitriptyline yesterday?

Please choose **only one** of the following:

- ☐ Yes
- ☐ No

ANY OTHER COMMENTS?

We're really interested in the positive and negative effects that benzodiazepines have on people's lives. The questionnaire can't capture all of this, so if there are any other comments you would like to make, please let us know in the space below.

Please write your answer here:

Thank you for completing this survey. Your participation is greatly appreciated.

Study completion is estimated for 2014; for information on general study results please contact Aneliese at apoorter@utas.edu.au after this date.

To thank you for your participation, you can choose to enter a competition to win one of three *$500 Coles Myer Vouchers*.

Please enter the prize draw by clicking on the link below